

TRANSMITTAL LETTER TO THE UNITED STATES

537-1064

DESIGNATED/ELECTED OFFICE (DO/EO/US)

U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR 1.5)

CONCERNING A FILING UNDER 35 U.S.C. 371

10/019741

INTERNATIONAL APPLICATION NO.

INTERNATIONAL FILING DATE

PRIORITY DATE CLAIMED

PCT/GB00/02491

June 23, 2000

June 28, 1999

TITLE OF INVENTION

Optical fibre Probe for Photoacoustic Material Analysis

APPLICANT(S) FOR DO/EO/US

Timothy Noel Mills, Paul Beard and David Delpy

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information.

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☐ This is an express request to begin national examination procedures (35 U.S.C. 371(f)). The submission must include items (5), (6), (9) and (24) indicated below.
4. ☒ The US has been elected by the expiration of 19 months from the priority date (Article 31).
5. ☒ A copy of the International Application as filed (35 U.S.C. 371 (c) (2))
 - a. ☐ is attached hereto (required only if not communicated by the International Bureau).
 - b. ☒ has been communicated by the International Bureau.
 - c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☐ An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)).
 - a. ☐ is attached hereto.
 - b. ☐ has been previously submitted under 35 U.S.C. 154(d)(4).
7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371 (c)(3))
 - a. ☐ are attached hereto (required only if not communicated by the International Bureau).
 - b. ☐ have been communicated by the International Bureau.
 - c. ☐ have not been made, however, the time limit for making such amendments has NOT expired.
 - d. ☒ have not been made and will not be made.
8. ☐ An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. ☐ An oath or declaration of the inventor(s) (35 U.S.C. 371 (c)(4)).
10. ☐ An English language translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371 (c)(5)).
11. ☐ A copy of the International Preliminary Examination Report (PCT/IPEA/409).
12. ☐ A copy of the International Search Report (PCT/ISA/210).

Items 13 to 20 below concern document(s) or information included:

13. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
14. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
15. ☒ A **FIRST** preliminary amendment.
16. ☐ A **SECOND** or **SUBSEQUENT** preliminary amendment.
17. ☐ A substitute specification.
18. ☐ A change of power of attorney and/or address letter.
19. ☐ A computer-readable form of the sequence listing in accordance with PCT Rule 13ter.2 and 35 U.S.C. 1.821 - 1.825.
20. ☐ A second copy of the published international application under 35 U.S.C. 154(d)(4).
21. ☐ A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4).
22. ☐ Certificate of Mailing by Express Mail.
23. ☐ Other items or information.

U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR 1.5) 10/019741	INTERNATIONAL APPLICATION NO. PCT/GB00/02491	ATTORNEY'S DOCKET NUMBER 537-1064
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24. The following fees are submitted.				CALCULATIONS PTO USE ONLY	
BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)) :					
<input type="checkbox"/> Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO				\$1040.00	
<input checked="" type="checkbox"/> International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO				\$890.00	
<input type="checkbox"/> International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO				\$740.00	
<input type="checkbox"/> International preliminary examination fee (37 CFR 1.482) paid to USPTO but all claims did not satisfy provisions of PCT Article 33(1)-(4)				\$710.00	
<input type="checkbox"/> International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfied provisions of PCT Article 33(1)-(4)				\$100.00	
ENTER APPROPRIATE BASIC FEE AMOUNT =				\$890.00	
Surcharge of \$130.00 for furnishing the oath or declaration later than <input type="checkbox"/> 20 <input type="checkbox"/> 30 months from the earliest claimed priority date (37 CFR 1.492 (e)).				\$0.00	
CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE		
Total claims	6 - 20 =	0	x \$18.00	\$0.00	
Independent claims	1 - 3 =	0	x \$84.00	\$0.00	
Multiple Dependent Claims (check if applicable).			<input type="checkbox"/>	\$0.00	
TOTAL OF ABOVE CALCULATIONS =				\$890.00	
<input checked="" type="checkbox"/> Applicant claims small entity status. See 37 CFR 1.27). The fees indicated above are reduced by 1/2				\$445.00	
SUBTOTAL =				\$445.00	
Processing fee of \$130.00 for furnishing the English translation later than <input type="checkbox"/> 20 <input type="checkbox"/> 30 months from the earliest claimed priority date (37 CFR 1.492 (f)).				\$0.00	
TOTAL NATIONAL FEE =				\$445.00	
Fee for recording the enclosed assignment (37 CFR 1.21(h)) The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31) (check if applicable).			<input type="checkbox"/>	\$0.00	
TOTAL FEES ENCLOSED =				\$445.00	
				Amount to be: refunded	\$
				charged	\$

- a. ☒ A check in the amount of **\$445.00** to cover the above fees is enclosed
- b. ☐ Please charge my Deposit Account No. _____ in the amount of _____ to cover the above fees. A duplicate copy of this sheet is enclosed
- c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. **12-0913** A duplicate copy of this sheet is enclosed.
- d. ☐ Fees are to be charged to a credit card. **WARNING:** Information on this form may become public. **Credit card information should not be included on this form.** Provide credit card information and authorization on PTO-2038.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

William M. Lee, Jr.
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SIGNATURE

William M. Lee, Jr.

NAME

26,935

REGISTRATION NUMBER

12-28-01

DATE

537-1064

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE THE APPLICATION OF

Mills

SERIAL NO.:

FILED:

FOR: OPTICAL FIBRE PROBE FOR
PHOTOACOUSTIC MATERIAL
ANALYSIS

)
) Examiner:
)
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) Group Art Unit:
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)
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AMENDMENT ACCOMPANYING APPLICATION

Honorable Director of Patents
and Trademarks
Washington, D.C. 20231

Dear Sir:

The present application is the national filing of International Application No. PCT/GB00/02491. Before calculation of the national filing fee for the United States, it is requested that the application be amended as follows:

In the claims:

Amend claims 4 - 6 as follows:

4. (amended). A probe as claimed in claim 1, wherein the outer diameter of the outer core is approximately 250 μm .
5. (amended). A probe as claimed in claim 1, wherein the interferometer film is butted against the second end of the fibre.

6. (amended). Medical examination equipment for characterising biological tissue comprising a probe as claimed in claim 1 and means for displaying the detected modulated reflected signal.

REMARKS

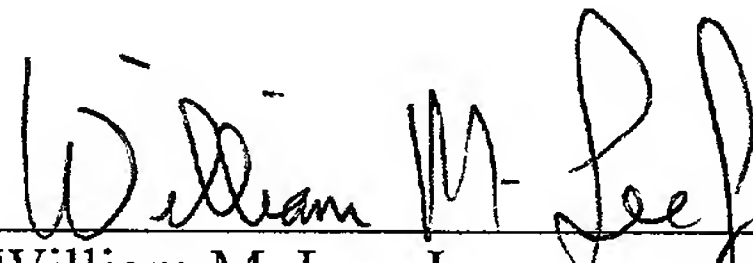
The above amendments are being made in order to eliminate multiple dependency and improper multiple dependency from the international application before calculation of the national filing fee for the United States. Should any multiple dependency remain, that is unintended, and the Patent and Trademark Office is requested to cancel any remaining multiple dependent claims without prejudice before calculation of the national filing fee for the United States.

The International Preliminary Examination Report reaches the conclusion that claims 1 - 6 meet the requirements of novelty and inventive step (nonobviousness). It is submitted that the same result should occur in the United States.

Examination of the Application on its merits is awaited.

Dated: December 28, 2001

Respectfully submitted,



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[illegible]

4. (amended). A probe as claimed in [any preceding] claim 1, wherein the outer diameter of the outer core is approximately 250 μm .
5. (amended). A probe as claimed in [any preceding] claim 1, wherein the interferometer film is butted against the second end of the fibre.
6. (amended). Medical examination equipment for characterising biological tissue comprising a probe as claimed in [any preceding] claim 1 and means for displaying the detected modulated reflected signal.

OPTICAL FIBRE PROBE FOR PHOTOACOUSTIC MATERIAL ANALYSIS

This invention relates to optical fibre probes for the excitation of a sample to produce signals for analysis. These signals may comprise photoacoustic and/or photothermal waves.

Such probes have been proposed for characterising arterial tissue prior to treatment of narrowed blood vessels, for example caused by atheroma. Pulsed laser signals have been proposed as the excitation signal, which result in the generation of an acoustic signal through thermal expansion effects within the sample. Excitation signals of different wavelengths have been proposed in order to generate a photoacoustic signature which conveys different types of information concerning the sample.

For example, it has been found that the photoacoustic signals generated by laser excitation of wavelength around 450nm (e.g. 436 and 461nm) may be analysed to detect the presence of atheroma, based on the different attenuations of the excitation signal in the atheroma and in normal tissue. Alternatively, an excitation signal of longer wavelength, for example 530nm, may be employed to enable thickness measurement of the sample. At this wavelength, the excitation signal penetrates through the sample, and timing analysis of the signals generated at the boundaries of tissue layers enables a thickness calculation to be performed.

Analysis of arterial tissue using pulsed laser excitation to generate acoustic and thermal signals is discussed in detail in the article "Characterization of post mortem arterial tissue using time-resolved photoacoustic spectroscopy at 436, 461 and 532 nm" in Phys. Med. Biol. 42 (1997) pages 177-198.

A design of optical fibre probe suitable for sample analysis as described above is disclosed in the article "Optical fiber photoacoustic-photothermal probe" published in Optics Letters Vol. 23, No. 15 of 1 August 1998. The probe comprises a multimode optical fibre with a transparent Fabry-Perot polymer film sensor mounted at its distal end, which is placed in contact with the sample for analysis. Optical pulses are launched into the fibre and absorbed in the target resulting in the generation of ultrasonic thermoelastic waves for detection by the sensor.

5 A problem with the probe design described above is that the wavelength of the generated acoustic signal may be small compared to the diameter of the sensing region which is defined by the core diameter of the multimode fibre. As a result, the interferometer may not detect signals with oblique entry angles, for example edge wave signals that arise due to diffraction effects.

According to the invention, there is provided a probe for the excitation of a sample to produce an acoustic signal and for analysis of the signal, comprising:

an excitation source which provides a pulsed laser output;

10 an optical fibre having a central inner core, a concentric outer core and an outer cladding, the pulsed laser output being supplied to the outer core at a first end of the optical fibre, the second end of the optical fibre being provided with an interferometer film which is substantially transparent to the laser pulses, a signal produced in the sample modulating the thickness of the film; and

15 a light source and detector assembly which provides an interferometer signal to the inner core at the first end of the fibre and detects the modulated reflected signal received from the inner core.

20 The probe of the invention has a small inner core which acts as the sensing part of the probe, but has a larger concentric outer core for carrying the laser excitation pulses. The probe is therefore able to carry the required energy signal for excitation of the sample, but also provides a small sensing area defined by the central inner core. This increases the frequency range of signals which can be detected at non-normal angles of incidence. Accordingly the sensitivity of the device is increased to changes in the temporal characteristics of the signal.

25 The signal may comprise an acoustic wave or thermal wave.

30 Preferably, the inner core is a single mode fibre, which may have a diameter of less than $10\mu\text{m}$ and preferably around $6\mu\text{m}$. This may result in an analysis probe having an active area of less than $10\mu\text{m}$. This enables the analysis function of the probe to be responsive to plane wave components and edge wave components of the generated acoustic signal.

One possible use of the probe is in medical examination equipment for characterising

biological tissue, for example arterial tissue.

The invention will now be described by way of example, with reference to and as shown in the accompanying drawing which shows a probe of the invention in use for analysing a sample.

The figure shows a sample 10 for analysis using the probe 12 of the invention. The probe 12 comprises an optical fibre 14 having a cleaved and polished end face 16 against which a polymer interferometer film 18 is provided. The polymer film 18 is transparent so that laser excitation pulses, represented schematically as arrows 20 in the figure, may be introduced into the sample 10 through the film 18. These pulses 20 may comprise nanosecond, submillijoule optical pulses which are absorbed in the biological sample 10, thereby producing thermal waves with a typical duration of the order of a few hundred milliseconds. Rapid thermal expansion occurs within the sample 10 generating ultrasonic thermoelastic waves with a typical duration of several hundred nanoseconds. The thermoelastic waves comprise an acoustic signal 22 which modulates the thickness of the film 18. Of course, other excitation signals may be used, depending upon the nature of the sample under analysis.

The interferometer defined by the film 18 is illuminated by light launched into the fibre from a continuous wave low-power laser source. The acoustic wave 22 modulates the thickness of the film 18 and hence the optical phase difference between the reflections from the two sides of the film. Similarly, the thermal waves modulate the optical thickness of the film which is also detectable as a result of the optical phase differences. In each case, a corresponding intensity modulation in the light reflected from the sensing film is produced, which is then detected. The reflections take place at the two faces of the film 18, as a result of the refractive index mismatch at the two sides of the film. Wavelength-selective dielectric reflective coatings may be applied to the faces of the film 18, which are transparent to the excitation pulses but reflective to the wavelength of the continuous wave signal. Shown schematically in the figure is an incident light signal 24 and the two reflected signals 26, 28.

The laser excitation pulses 20 are produced by a frequency-doubled Q-switched Nd:YAG laser operating at 532nm or by a tuneable dye laser. The laser forms part of an excitation source and light source/detector assembly 30, which also provides the continuous wave output for interrogation of the interferometer. This continuous wave output may be derived from a tuneable continuous wave source such as a laser diode.

The excitation pulses 20 may have a wavelength which is selected in dependence upon the desired characteristic of the sample 10 to be analysed and upon the nature of the sample. For example, the pulses may have a wavelength which is such that they penetrate the entire thickness of the sample 10. In this case thermoelastic waves will be generated at the two surfaces of the sample 10, and the detector assembly may then enable the thickness of the sample to be calculated. Alternatively, an excitation wavelength could be chosen to generate different thermoelastic signals depending upon the attenuation characteristics of the sample 10, which may enable an operator to distinguish between normal and abnormal biological tissue, for example normal and abnormal arterial tissue.

The detector assembly of the unit 30 may comprise a silicon pin photodiode, the output of which is preferably displayed on an oscilloscope.

To the extent described above, the construction of the probe is known. In accordance with the invention, the optical fibre 14 comprises a central inner core 40, a concentric outer core 42 and an outer cladding 44. Such double-core concentric fibres are known for use in other applications, such as optical fibre lasers and laser amplifiers. The method of constructing such a fibre will not therefore be described. The pulsed laser output 20 is supplied to the outer core 42 by the unit 30, whereas the interrogation signal 24 is provided by the unit 30 to the inner core 40. The modulated reflected signal provided by the interferometer film 18 is transmitted down the inner core 40 to the detector part of the unit 30.

The spot size of the interrogating continuous wave source is focused to match the core diameter of the inner fibre, and the spot size of the excitation pulses matches the outer fibre diameter. Some energy from the excitation pulses will travel down the central core, but the selection of different wavelengths for the excitation signal and the interrogation signal will

enable the detector 30 to distinguish between those signals using spectral analysis.

Conventional apparatus may be employed to launch the excitation and interrogation signals into the fibre, for example using half-silvered mirrors to combine the signals from the two sources.

The inner core 40 preferably defines a single mode fibre, with the outer core 42 acting as cladding of the inner core. For this purpose, the inner core 40 has a higher refractive index than the outer core 42. The outer core 42 is capable of carrying higher energy signals, and the surrounding cladding 44 has a lower refractive index than the outer core 42.

The inner core 40 preferably has a diameter of 5-10 μ m, whereas the outer core has a diameter of approximately 250 μ m.

The use of a physically small, and preferably single mode, inner core as the transport medium for the interferometer signals enables the sensing device to have a small active area. This enables the device to detect input signals of a wide range of wavelengths at non-normal angles of incidence. Input signals entering the sensor at an angle to the longitudinal axis of the sensor will be integrated over the active area of the sensor, and as a result a smaller active area improves the directional characteristics of the sensor. The excitation signal causes the sample to produce plane wave and edge wave components. The edge wave component is a rarefaction wave generated at the outside edge of the envelope of the excitation signal. The edge wave and plane wave components carry different information concerning the sample being analysed. The probe of the invention enables the edge wave components, which enter the probe at an oblique angle, to be detected due to the small active area which reduces band limiting of the probe response. The edge wave components will always enter the probe at an oblique angle, irrespective of the direction faced by the probe, as they result from the edge of the excitation signal produced by the probe. Furthermore, the physical spacing between the outside of the outer core and the inner core enables the probe to separate the plane wave and edge wave signals from the combined signal received by the probe. This separation may be achieved by temporal analysis.

The acoustic signals 22 produced in the sample 10 may typically have frequencies up to 30 MHz, and for acoustic signals travelling in fresh water this corresponds to a wavelength of $47\mu\text{m}$. Preferably, therefore, the active area of the sensor is less than $20\mu\text{m}$, so that the sensor can be responsive to 30 MHz acoustic signals. The detection bandwidth then exceeds the range of frequencies of the input signal, the sensor having omnidirectional response.

A single mode fibre is not able to carry the required Q-switched laser pulses for the excitation of the sample, and these are provided in the outer core 42. The larger area of the outer core 42 enables an excitation wave to be introduced into the sample 10 over a much greater area than the sensor area defined by the central inner core 40.

The small active area of the interferometer also facilitates the production of a polymer film 18 having extremely parallel and uniform opposite faces over the area of interest of the sensor. The sensing film may comprise a disc of PET (polyethylene terephthalate). Such discs may be cut from a larger film, and the smaller the required area the more uniform will be the film thickness.

The design of the excitation source and light source/detector assembly 30 will be apparent to those skilled in the art, and specific examples have been given above. Thus, the light source may comprise a tuneable laser diode which may produce light of around 850nm, and it may be tuned to obtain quadrature operation of the interferometer. The detector assembly may comprise a photodiode, as discussed above, and may have an integral transimpedance amplifier.

There are various possible applications in which the probe of the invention may be used, in addition to the analysis of biological tissue. Such applications may include medical as well as non-medical sample analysis.

Claims

1. A probe for the excitation of a sample to produce an acoustic signal and for analysis of the signal, comprising:

an excitation source which provides a pulsed laser output;

an optical fibre having a central inner core, a concentric outer core and an outer cladding, the pulsed laser output being supplied to the outer core at a first end of the optical fibre, the second end of the optical fibre being provided with a interferometer film which is substantially transparent to the laser pulses, a signal produced in the sample modulating the thickness of the film; and

a light source and detector assembly which provides an interferometer signal to the inner core at the first end of the fibre and detects the modulated reflected signal received from the inner core.

2. A probe as claimed in claim 1, wherein the inner core defines a single mode fibre.

3. A probe as claimed in claim 2, wherein the diameter of the inner core is less than $10\mu\text{m}$.

4. A probe as claimed in any preceding claim, wherein the outer diameter of the outer core is approximately $250\mu\text{m}$.

5. A probe as claimed in any preceding claim, wherein the interferometer film is butted against the second end of the fibre.

6. Medical examination equipment for characterising biological tissue comprising a probe as claimed in any preceding claim and means for displaying the detected modulated reflected signal.

(19) World Intellectual Property Organization
International Bureau



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(22) International Filing Date: **23 June 2000 (23.06.2000)**

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(84) Designated States (*regional*): ARIPO patent (GH, GM,
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(72) Inventors; and

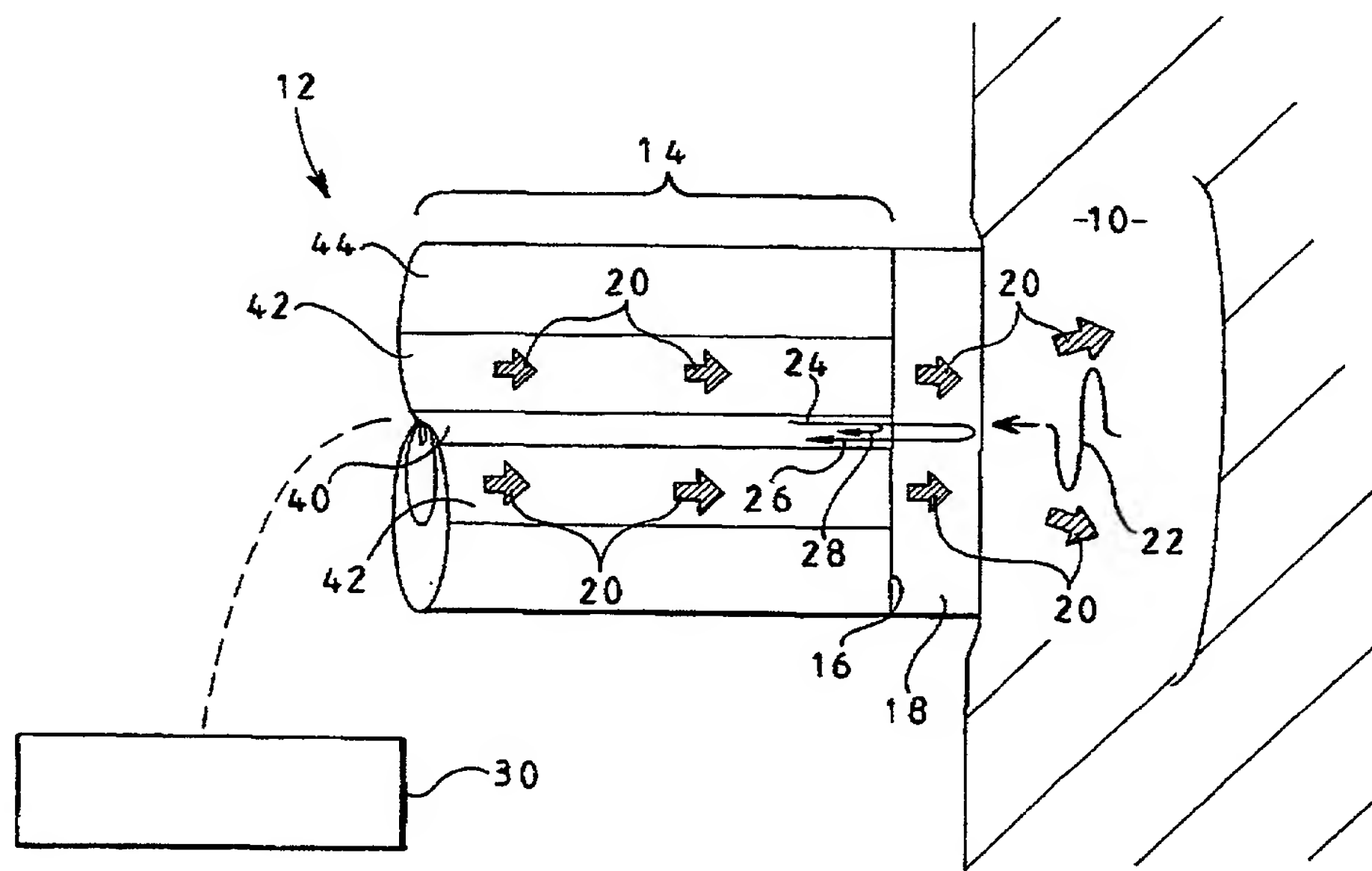
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Published:

— *With international search report.*

[Continued on next page]

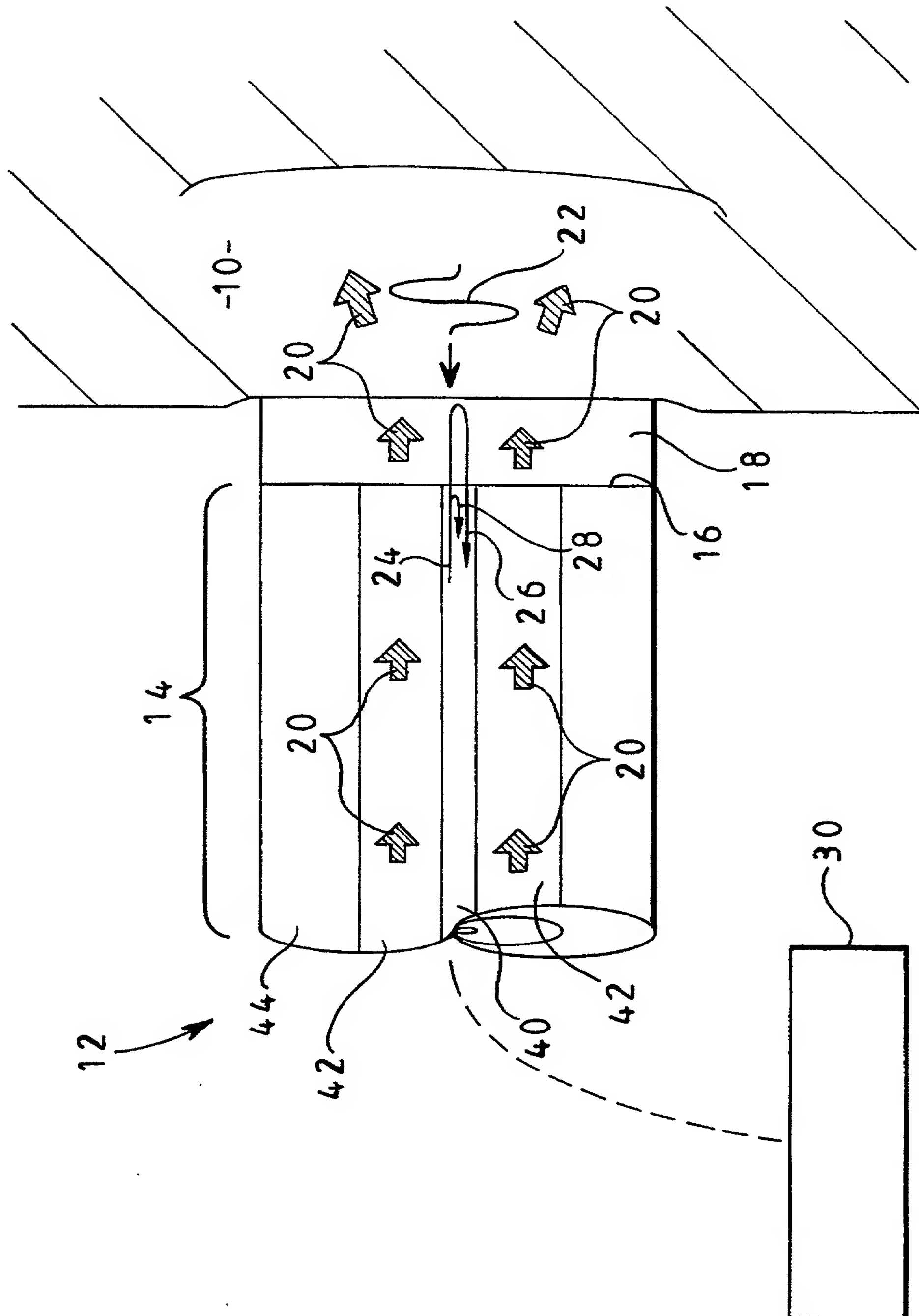
(54) Title: **OPTICAL FIBRE PROBE FOR PHOTOACOUSTIC MATERIAL ANALYSIS**



(57) Abstract: A probe comprises an excitation source and a double-core optical fibre. A pulsed laser signal (20) of the excitation source is supplied to the outer core (42) at one end of the optical fibre. The other end is provided with an interferometer film (18). An excitation signal (22) produced in the sample (10) modulates the thickness of the film (18). This provides an interferometer signal (26, 28) detected from the inner core (40).

WO 01/01111 A1


10/019741



Smith, McWilliams, Sweeney & Ohlson, P.O. Box 2786, Chicago, Illinois 60690-2786,
telephone number (312) 368-1300.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Full name of sole or first inventor: TIMOTHY NOEL MILLS

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Date 15/1/01

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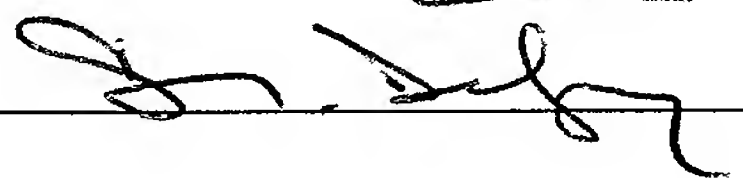
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PRIOR FOREIGN APPLICATION(S)

Country	Number	Date Filed	Priority Claimed	
			Yes	No
Great Britain	9915082.3	June 28 1999	x	

I hereby claim the benefit under Title 35, United States Code Section 120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, Section 112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, Section 1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application.

Application Serial No.	Filing Date	Status
PCT/GB00/02491	23 June 2000	Pending

And I hereby appoint William M. Lee, Jr., Registration No. 26,935, Thomas E. Smith, Registration No. 18,243, Dennis M. McWilliams, Registration No. 25,195, James R. Sweeney, Registration No. 18,721, Glenn W. Ohlson, Registration No. 28,455, David C. Brezina, Registration No. 34,128, Jeffrey R. Gray, Registration No. 33,391, Gerald S. Geren, Registration No. 24,528, Timothy J. Engling, Registration No. 39,970, Peter J. Shakula, Registration No. 40,808, Robert F. I. Conte, Registration No. 20,354, Howard B. Rockman, Registration No. 22,190, John W. Hayes, Registration No. 19,286, and Mark A. Hagedorn, Registration No. 44,731, to prosecute this application and to transact all business in the Patent and Trademark Office connected herewith. It is requested that all communications be directed to Lee, Mann,

14

DECLARATION AND POWER OF ATTORNEY FOR PATENT APPLICATION

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled OPTICAL FIBRE PROBE FOR PHTOACOUSTIC MATERIAL ANALYSIS, the specification of which:

— is attached hereto.

X was filed on 23 June 2000 as

Application Serial No. PCT/GB00/02491 and

was amended on _____ (if applicable).

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, Section 1.56(a).

I hereby claim foreign priority benefits under Title 35, United States Code, Section 119 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

5

LASER OPTO-ACOUSTIC IMAGING SYSTEM

10

BACKGROUND OF THE INVENTION

Field of the Invention

The present invention relates generally to the fields of optics, lasers and medical diagnostic devices. More specifically, the present invention relates to a laser opto-acoustic imaging system capable of producing a three-dimensional image (tomography scan) of human organs.

Description of the Related Art

Ultrasonic imaging is currently used widely in clinical medical practice to detect abnormalities in soft tissue organs with acoustic boundaries such as one type of tissue embedded within another type. Ultrasonic imaging has, however, several limitations. For example, ultrasonic imaging is incapable of detecting acoustically homogeneous tissues, i.e., when ultrasonic properties of all of the tissues scanned are similar).

Optical imaging technologies are based on time-resolved or phase-resolved detection of diffusely reflected light pulses or photon density waves. Optical tomographic technologies take advantage of differences in tissue optical properties for diagnostic purposes. However, ubiquitous light scattering in tissues has been a great obstacle to laser imaging.

Optoacoustic spectroscopy methods utilize light to excite an object of interest (molecules or atoms). Using acoustic (piezoelectric) detectors, optoacoustic spectroscopy methodology can measure stress amplitude for obtaining absorption spectra. This represents not an imaging or tomographic technology per se.

Principles of laser optoacoustics, i.e., methods of stress generation and detection have been described. Relationships between spatial distribution of acoustic sources and temporal profile of laser-induced stress waves have been derived. However, methods of laser optoacoustics have not been proposed as means for medical diagnostics.

The prior art is deficient in the lack of functional laser opto-acoustic imaging system. The present invention fulfills this longstanding need and desire in the art.

SUMMARY OF THE INVENTION

Photo-acoustic ultrasound technology for medical imaging has been described in the prior art. However, the prior art has not understood and correctly manipulated three principles of laser optoacoustic imaging important for sensitivity, spatial resolution and correct interpretation of images. These principles are: (1) short-pulse laser irradiation to generate transient stress waves under conditions of temporal stress confinement. Such irradiations provides the highest possible amplitude of generated stress with profiles resembling that of light distribution in tissues, which yields sharp images with accurate localization; (2) time-resolved detection of a stress profile for obtaining diagnostic information not from the fact of any signal detection, but from the temporal profile of generated stress wave; (3) use of wide-band piezoelectric detectors to correctly reproduce stress profiles (acoustic waves with wide spectrum of ultrasonic frequencies) to obtain high spatial resolution of tomography. The laser opto-acoustic imaging system (LOAIS) of the present invention partially combines elements of (1) ultrasonic scanning, (2) optical time-resolved tomography and (3) selective pulsed excitation of tissue heterogeneous structures and time-resolved detection of laser-induced stress waves for obtaining detailed medical diagnostic information.

The present invention is directed to both a technique and a device and can be used to image a complex tissue structure on the basis of optical contrast. The technique of the present

invention uses a pulsed laser to slightly but quickly heat a specific tissue region with an optical absorption that differs relative to its surroundings. This slight heating converts to a pressure wave, i.e., a sound wave which propagates outward from the source of the heating. A transducer detects the time, magnitude and shape of the arriving pressure waves. The transducer may be a piezoelectric transducer at the tissue surface or an imbedded transducer. The laser pulse must be sufficiently short to allow the pressure to build up before the pressure can dissipate at the speed of sound (approximately 1500 m/s). For example, a 10-ns laser pulse can image absorbing objects with the spatial resolution of $(1500 \text{ m/s}) (10 \text{ ns}) = 15 \text{ } \mu\text{m}$. Thus, the invention allows imaging of tissue structures with high spatial resolution within turbid media such as biological tissues. The imaging techniques of the present invention are based on optical contrast rather than density changes such as in ultrasound, magnetic resonance imaging or x-ray computed tomography. The method of the present invention, therefore, can be used to image contrast objects not well imaged by these other state of the art imaging techniques.

In one embodiment of the present invention, there is provided a method of diagnosing a diseased tissue within a normal tissue using laser optoacoustic tomography, comprising the steps of: irradiating the surface of the normal tissue with at least one laser pulse so as to penetrate to a sufficient depth and selectively heat a small volume or layer of diseased tissue with a higher optical absorption; causing the diseased tissue to produce a stress wave with a profile resembling that of diseased tissue, said stress wave propagates with minimal alterations to the surface of normal tissue; detecting said stress wave with at least one acoustic transducer; recording the amplitude and temporal profile of laser-induced stress wave by digital oscilloscope; analyzing the amplitude and temporal profile of laser-induced stress wave with a computer.

In another embodiment of the present invention, there is provided a novel device as a tomography system for biomedical diagnostics comprising: a pulsed laser; a light delivery system; at least one acoustic detector; an electronic system for signal

recording and processing; and a computer with software for image reconstruction and analysis.

Other and further aspects, features, and advantages of the present invention will be apparent from the following description of the presently preferred embodiments of the invention given for the purpose of disclosure.

BRIEF DESCRIPTION OF THE DRAWINGS

10 So that the matter in which the above-recited features, advantages and objects of the invention, as well as others which will become clear, are attained and can be understood in detail, more particular descriptions of the invention briefly summarized above may be had by reference to certain embodiments thereof
15 which are illustrated in the appended drawings. These drawings form a part of the specification. It is to be noted, however, that the appended drawings illustrate preferred embodiments of the invention and therefore are not to be considered limiting in their scope.

20 Figure 1 shows a schematic of the laser optoacoustic tomography system in transmission mode.

Figure 2 shows that an acoustic transducer signal can be detected *in vitro* from small volume of liver placed inside large volume of chicken breast muscle tissue.

25 Figure 3 shows that an acoustic transducer signal can be detected from a phantom pathologic tissue (2.5 mm colored gel sphere) embedded within large volume of optically turbid gel cylinder simulating woman's breast. Signal recorded from gel cylinder in case when laser pulse misses and therefore does not
30 heat small color sphere is also presented for comparison.

Figure 4 shows a schematic of laser optoacoustic tomography in reflection mode.

Figure 5 shows an acoustic transducer signal detected
35 *in vivo* from chicken cockscomb best known model for port-wine stains.

Figure 6 shows an acoustic transducer signal detected *in vivo* from small tumor located underneath the skin of mouse's lower back.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

5 As used herein, the term "laser optoacoustic tomography" refers to a laser optoacoustic tomography system that employs detection of stress waves reflected from the volume of their generation back to the irradiated tissue surface. In other words, laser optoacoustic tomography is a diagnostic procedure to obtain optical images of layered tissue while detecting laser
10 induced stress profiles.

As used herein, the term "tomography in reflection transmission mode" refers to the laser optoacoustic tomography system of the present invention that employs the detection of stress waves transmitted from the volume of their generation to
15 rear tissue surfaces, i.e., opposite to irradiated.

As used herein, the term "transient stress waves" refers to a stress wave that has limited duration and occupies limited volume.

As used herein, the term "temporal stress
20 confinement" refers to the confinement of laser-induced stress within heated volume during the course of laser energy deposition.

As used herein, the term "time-resolved detection of stress profile" refers to the detection of transient stress waves
25 with temporal resolution sufficient to reconstruct a pressure wave profile with precision.

As used herein, the term "optical time-resolved tomography" refers to a tomography based on time-resolved detection of ultrashort laser pulses transmitted through biological
30 tissue of diagnostic interest.

As used herein, the term "piezoelectric detectors" refers to detectors of acoustic, e.g., stress waves utilizing the principle of electric charge generation upon a change of volume within crystals subjected to a pressure wave.

35 As used herein, the term "ultrasonic scanning" refers to a diagnostic procedure that employs delivery of ultrasonic stress waves to a tissue surface followed by the detection of the signals reflected from boundaries within the tissue under diagnosis.

As used herein, the term "pulsed heating of tissue" refers to the heating of a tissue volume irradiated with laser pulses.

The present invention utilizes the time-resolved detection of laser-induced stress (ultrasonic) waves to obtain tomography images of human organs or cellular structures for diagnostic purposes. Diagnostic procedures in which the laser opto-acoustic imaging system of the present invention are useful include: (1) short laser pulses delivered to the front surface of human organ under investigation. Laser wavelength must be selected to achieve desirable light penetration depth and maximum contrast between normal and abnormal tissues. Heterogeneous absorption of photons and heating of tissue causes generation of thermo-elastic stress that is temporarily confined in the irradiated volume. Short laser pulses serve three purposes: (1) obtain the most effective generation of transient stress, (2) obtain a stress profile which resembles the profile of heterogeneous light distribution, (3) to obtain images with ultimate accuracy of localization of tissue layer or volume of diagnostic interest.

Transient stress waves will propagate toward acoustic transducer (detector). A transducer, e.g., a piezoelectric transducer, will convert the stress profile into an electrical signal. The temporal profile of the electrical signal recorded by a digital oscilloscope is converted into a spatial profile of a transient stress distribution. Transient stress distribution resembles a profile of absorbed laser energy distribution, which in turn carries certain diagnostic information. Both a laser beam and a piezoelectric transducer (detector) are scanned over the area under diagnosis. Positioning of a detector at various locations permits reconstruction of a three dimensional opto-acoustic image from transient stress profiles and time-delays between moments of laser pulsed irradiation and moments of stress detection (the speed of acoustic waves propagation is known for vast majority of tissues). Stress detection can be performed in both, the transmission mode and the reflection mode, which allows substantial flexibility for *in vivo* diagnostics of various human organs and other biological systems.

Laser opto-acoustic imaging systems (LOAIS) can be used in diagnostic screening of breast cancer (mammography), skin tumors and various other lesions (like port-wine stains etc.) whether accessible externally or via endoscopes, detection of brain hematomas (hemorrhages), atherosclerotic lesions in blood vessels, and for general characterization of tissue composition and structure. In addition, laser opto-acoustic imaging can provide feedback information during laser medical treatments.

Thus, the present invention is directed to a method of diagnosing a diseased tissue within a normal tissue using laser optoacoustic tomography, comprising the steps of: irradiating the surface of the normal tissue with at least one laser pulse so as to penetrate to a sufficient depth and selectively heat a small volume or layer of diseased tissue with a higher optical absorption; causing the diseased tissue to produce a stress wave with a profile resembling that of diseased tissue, said stress wave propagates with minimal alterations to the surface of normal tissue; detecting said stress wave with at least one acoustic transducer; recording the amplitude and temporal profile of laser-induced stress wave by digital oscilloscope; analyzing the amplitude and temporal profile of laser-induced stress wave with a computer.

Preferably, the stress profiles are recorded and analyzed by the computer to reconstruct a three-dimensional image. Generally, the laser pulse heats certain tissue structures with different light absorption thereby generating stress profiles resembling profiles of absorbed laser energy distribution in heterogeneous tissues followed by time-resolved detection of ultrasonic stress waves. The shape and dimensions of the diseased tissue volume or layer is generally determined from the temporal profile of laser-induced stress, the time of stress wave arrival to the acoustic transducer, and the direction of the stress detection.

Preferably, the acoustic transducer is a piezoelectric detector and the acoustic transducer uses temporal resolution. Ordinarily, the transducer determines the geometry of the diagnosed tissue volume without scanning of acoustic transducer at a fixed location of the laser beam. However, multiple separate optical fibers or laser beams can be used to irradiate large volume of tissue to reduce time of scanning and incident laser fluence.

Generally, the amplitude and temporal profile of laser-induced stress wave is recorded by a digital oscilloscope.

5 In the methods of the present invention, stress detection can be in transmission mode and stress detection of tissue optical heterogeneities occurs at a tissue depth of up to about 12 cm. Alternatively, stress detection can be in reflection mode. Generally, the irradiating is in spectral range of therapeutic window from about 600 nm to about 1400 nm. It is further contemplated that one with ordinary skill in this art could use
10 exogenous molecular probes or dyes to enhance contrast of tomographic image.

Generally, the methods of the present invention may be used to diagnose a wide variety of diseased tissue. Preferably, the diseased tissue is breast carcinoma, brain hemorrhages,
15 hematomas, atherosclerotic plaques, polyarthritis, port-wine stains, skin disorders, melanomas or ocular diseases.

When the diseased tissue is an internal organ, the irradiation may be delivered via an endoscope and the acoustic transducer may be positioned on the skin surface. Alternatively,
20 the irradiation may be delivered onto the skin surface and the transducer is incorporated with an endoscope and positioned inside the organs. Further, when the diseased tissue is an internal organ, the optical fiber and transducer may be incorporated in endoscope and positioned inside the organs.

25 The present invention also provides a novel device as a tomography system for biomedical diagnostics comprising: a pulsed laser; a light delivery system; at least one acoustic detector; an electronic system for signal recording and processing; and a computer with software for image reconstruction and analysis.

30 The following examples are given for the purpose of illustrating various embodiments of the invention and are not meant to limit the present invention in any fashion.

With reference to the appended drawings, Figure 1 illustrates one embodiment of the present invention, i.e., an
35 example of the utility of laser optoacoustic tomography in diagnosing a small diseased tissue volume (black circle) within a large volume of normal tissue. The laser pulse irradiates the surface of the normal tissue and penetrates to a sufficient depth to

selectively heat a small volume of diseased tissue with a higher optical absorption. Instantly, the heated volume of diseased tissue produces a stress wave with a profile resembling that of diseased tissue. The stress wave propagates with minimal alterations to the surface of normal tissue where it is detected by an acoustic transducer with temporal resolution. The amplitude and temporal profile of laser-induced stress wave is recorded by digital oscilloscope and transferred via an interface to a computer for data analysis. Scanning of laser beam (optical fiber) allows the irradiation of the entire volume of the tomographically scanned organ and definite heating of any diseased tissues that exist within normal tissue. Scanning of the acoustic transducer along the surface of the organ permits a determination of the exact location of any diseased tissue volumes. The stress profiles are recorded and analyzed by the computer to reconstruct three dimensional images which can be displayed.

Tomography (imaging) in stress transmission mode utilizes detection of stress transients transmitted from the laser-excited volume toward the depth through thick layers of tissue. The emphasis in transmission mode tomography is made on sensitive detection of tissue optical heterogeneities located at substantial depth of tissue (up to 12 cm).

Figure 2 depicts an example of a measurement of laser-induced transient stress in a small piece of bovine liver tissue placed between muscle tissues slabs (chicken breast). Duration of the transient stress wave and amplitude were equal to 300 ns and 4 mbar, respectively, in accordance with sample thickness and optical absorption coefficient. This experiment demonstrated the ability of laser optoacoustic tomography to detect small volumes of tissue (3 mm x 2 mm x 0.5 mm) with absorption coefficient, $\mu_a = 0.215 \text{ cm}^{-1}$, that is slightly higher than that of surrounding tissue, $\mu_a = 0.09 \text{ cm}^{-1}$, at the depth of more than 4 centimeters.

Figure 3 shows an acoustic transducer signal detected from a phantom pathologic tissue (2.5 mm colored gel sphere) embedded within large volume of optically turbid gel cylinder. A control signal was used in case the laser irradiation "missed" the colored sphere and is also shown. The gel phantom simulated a woman's breast by having optical properties of a colored gel

sphere similar to those found in breast carcinoma. Moreover, the optical properties of the surrounding gel were similar to those in a woman's breast tissue. The geometry of the experiment is also shown. A laser pulse was delivered from one side of the gel cylinder and a transient stress wave was detected from the opposite side. The location of colored gel sphere which simulated the tumor was not known to the person who performed the diagnostic procedure. Simultaneous scanning of laser beam and acoustic transducer revealed both the location and dimensions of the "tumor".

Figure 4 shows a schematic diagram of the laser optoacoustic tomography of the present invention in the reflection mode embodiment of stress detection. A laser pulse irradiates the surface of tissue with a wavelength chosen to penetrate the tissue superficially (about 1 mm) and to heat selectively all microstructures within the tissue with the objective of obtaining high contrast and high spatial resolution. Instantly heated volume of layered tissue produces a stress wave that has profile indicating tissue structure. Stress waves were reflected toward the irradiated surface and were detected with minimal alterations by an acoustic transducer with nanosecond temporal resolution. Laser pulses were delivered to the same tissue surface where a stress wave was detected. The amplitude and temporal profile of a laser-induced stress wave was recorded by a digital oscilloscope and transferred via an interface to a computer for data analysis. Scanning by acoustic transducer-reflectometer with the laser beam permitted the irradiation of the entire area of diagnostic interest. Recorded stress profiles were analyzed by the computer to reconstruct a three dimensional image which was displayed and processed by special software.

Tomography (imaging) in stress reflection mode utilizes detection of stress transients generated in superficial tissue layer and reflected back toward tissue surface. The emphasis in reflection mode tomography is made on high spatial resolution of measured image (up to 1.5 μm).

Figure 5 depicts a z-axial optoacoustic image of absorbed laser fluence distribution in cock's comb. The transient stress profile induced by a 14-ns pulse at 532 nm in a cock's comb

of a rooster was measured *in vivo* by an acoustic transducer. The laser beam was about 1 cm in diameter. Time "0" corresponds to a signal detected from the tissue surface. Distinct layers were observed in the cock's comb tissue. Alteration of the detected stress transient due to diffraction of acoustic waves generated in distributed capillary blood vessels (layer 2) yields negative signal. When diffraction effects are compensated, or the transient stress measured under diffraction-free conditions such as in a layered system with homogeneous absorption within each layer, the stress profile will have only positive components. Signals 1-6, were induced in blood vessels, located at different depths in the tissue. Numbers 1-5 correspond to the acoustic transducer signals detected in layers with either enhanced density of small blood vessels (1 and 2) or in separated large blood vessels (3, 4 and 5). The layered structure of the cock's comb is clearly depicted (the layer with dense small dermal blood vessels that lies just below the epidermis, the layer of less vascular loose connective tissue, the comb core layer with arteries and veins that supply the more superficial vascular layers of the cockscomb). The depth of their location is measured correctly if compared with cockscomb histology. The lateral position can be found by scanning a focused laser beam along the tissue surface.

Figure 6 shows a display of a typical profile of a stress wave induced by nanosecond laser pulses at 532 nm in tissues of a mouse with a small tumor beneath the skin. Signals detected from the volume with cancer and from the tissue with no cancer are presented for comparison. The difference between two presented signals indicate that breast tumor can be diagnosed with laser optoacoustic tomography system of the present invention in a mice model *in vivo*. This is another example of laser optoacoustic tomography system of the present invention in the reflection embodiment performed *in vivo*. The object of study was a mouse with a cancer modeling female's breast tumor grown inside the muscle of the mouse. The imaging experiment was performed twice with two different mice with similar tumor conditions. These embodiments presented demonstrated laser optoacoustic imaging in tissues by time-resolved detection of laser-induced stress transients.

Any patents or publications mentioned in this specification are indicative of the levels of those skilled in the art to which the invention pertains. These patents and publications are herein incorporated by reference to the same extent as if each individual publication was specifically and individually indicated to be incorporated by reference.

One skilled in the art will readily appreciate that the present invention is well adapted to carry out the objects and obtain the ends and advantages mentioned, as well as those inherent therein. The present examples along with the methods, procedures, treatments, molecules, and specific compounds described herein are presently representative of preferred embodiments, are exemplary, and are not intended as limitations on the scope of the invention. Changes therein and other uses will occur to those skilled in the art which are encompassed within the spirit of the invention as defined by the scope of the claims.

WHAT IS CLAIMED IS:

1. A method of diagnosing a diseased tissue within a
5 normal tissue using laser optoacoustic tomography, comprising the steps of:

irradiating the surface of the normal tissue with at
least one laser pulse so as to penetrate to a sufficient depth and
selectively heat a small volume or layer of diseased tissue with a
10 higher optical absorption;

causing the diseased tissue to produce a stress wave
with a profile resembling that of diseased tissue, said stress wave
propagates with minimal alterations to the surface of normal
tissue;

15 detecting said stress wave with at least one acoustic
transducer;

recording the amplitude and temporal profile of laser-
induced stress wave by digital oscilloscope;

20 analyzing the amplitude and temporal profile of laser-
induced stress wave with a computer.

2. The method of claim 1, wherein said stress
profiles are recorded and analyzed by the computer to reconstruct
a three-dimensional image.

25 3. The method of claim 1, wherein said laser pulse
heats certain tissue structures with different light absorption
thereby generating stress profiles resembling profiles of absorbed
laser energy distribution in heterogeneous tissues followed by
30 time-resolved detection of ultrasonic stress waves.

4. The method of claim 1, wherein the shape and
dimensions of said diseased tissue volume or layer is determined
from the temporal profile of laser-induced stress, the time of stress
35 wave arrival to the acoustic transducer, and the direction of the
stress detection.

5. The method of claim 1, wherein the acoustic transducer is a piezoelectric detector.

6. The method of claim 1, wherein said stress wave is detected with an acoustic transducer using temporal resolution.

7. The method of claim 1, wherein said transducer determines the geometry of the diagnosed tissue volume without scanning of acoustic transducer at fixed location of laser beam.

8. The method of claim 1, wherein said multiple separate optical fibers or laser beams irradiate large volume of tissue to reduce time of scanning and incident laser fluence.

9. The method of claim 1, wherein said amplitude and temporal profile of laser-induced stress wave is recorded by a digital oscilloscope.

10. The method of claim 1, wherein said stress detection is in transmission mode.

11. The method of claim 1, wherein said stress detection of tissue optical heterogeneities occurs at a tissue depth of up to about 12 cm.

12. The method of claim 1, wherein said stress detection is in reflection mode.

13. The method of claim 1, wherein said irradiating is in spectral range of from about 600 nm to about 1400 nm.

14. The method of claim 1, wherein said irradiating is at a wavelength that corresponds to the absorption band of molecules, cells or tissues of diagnostic interest.

15. The method of claim 1, further comprising the use of exogenous molecular probes or dyes to enhance contrast of tomographic image.

16. The method of claim 1, wherein said diseased tissue is selected from the group consisting of breast carcinoma, brain hemorrhages, hematomas, atherosclerotic plaques, polyarthritis, port-wine stains, skin disorders, melanomas and ocular diseases.

17. The method of claim 1, wherein said diseased tissue is an internal organ, and wherein irradiation is delivered via endoscopes and said acoustic transducer is positioned on the skin surface.

18. The method of claim 1, wherein said diseased tissue is an internal organ, and wherein irradiation is delivered onto the skin surface and said transducer is incorporated with an endoscope and positioned inside the organs.

19. The method of claim 1, wherein said diseased tissue is an internal organ, and wherein an optical fiber and transducer are incorporated in endoscope and positioned inside the organs.

20. A tomography system for biomedical diagnostics comprising:
a pulsed laser;
a light delivery system;
at least one acoustic detector;
an electronic system for signal recording and processing; and
a computer with software for image reconstruction and analysis.

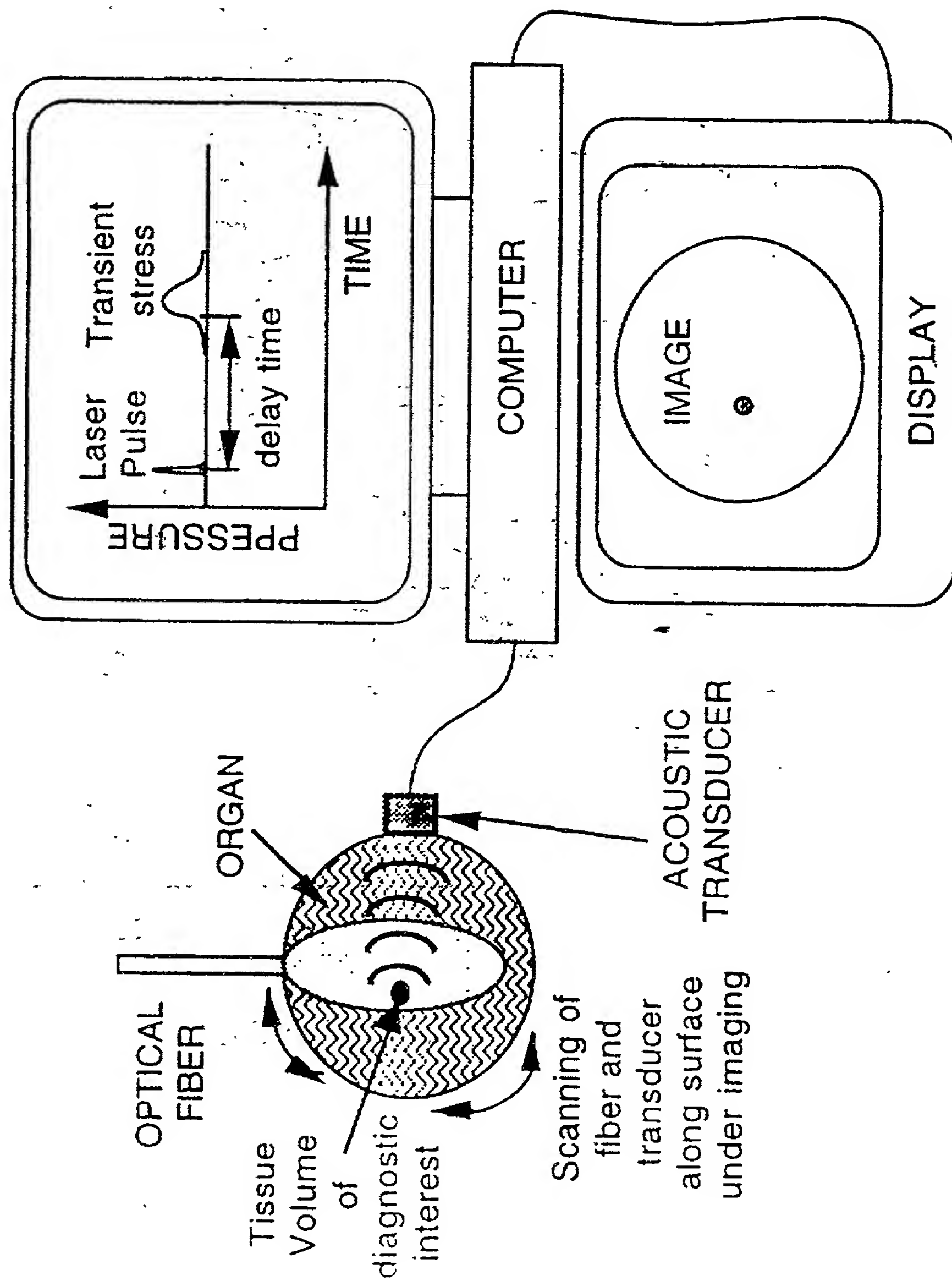


FIGURE 1

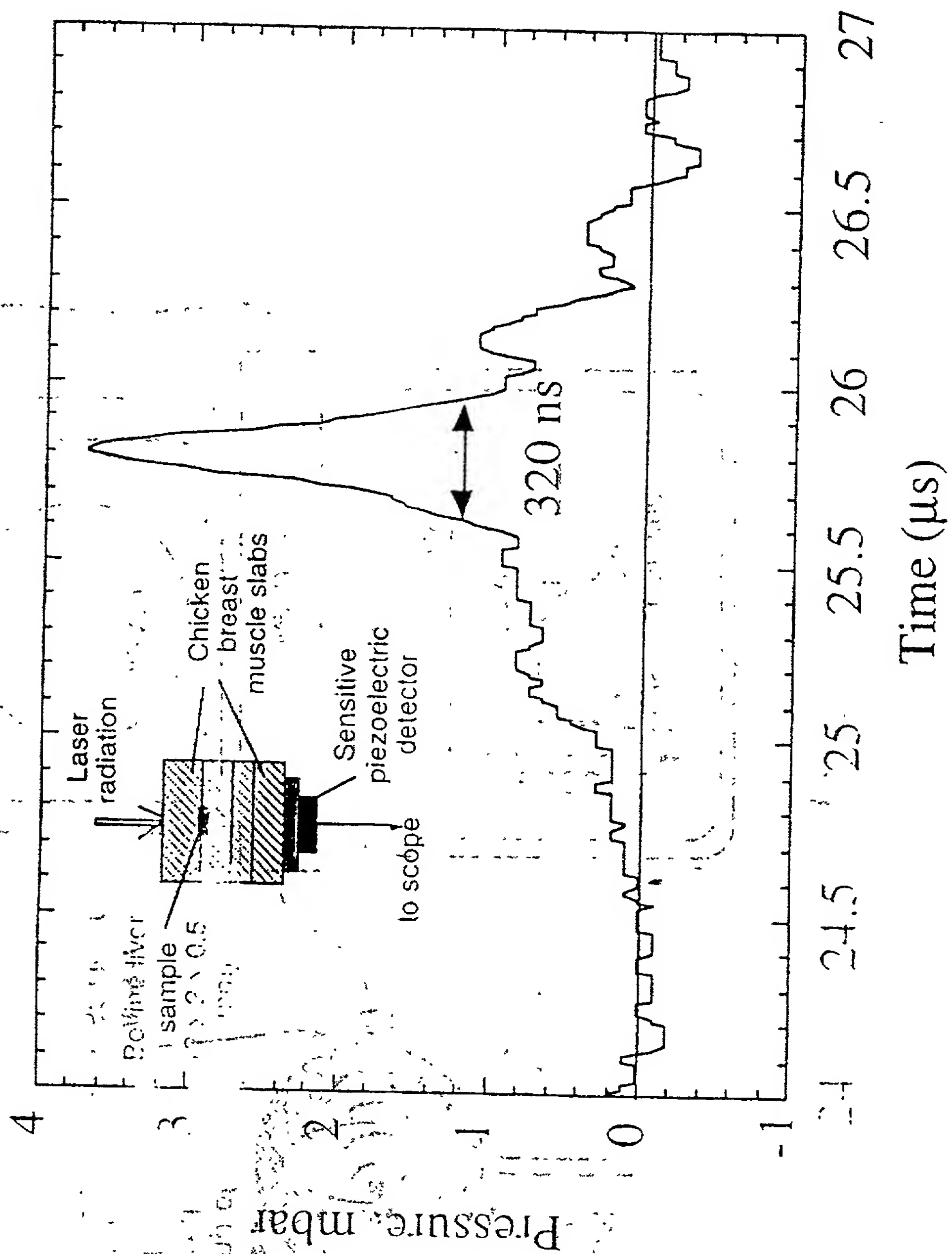


FIGURE 2

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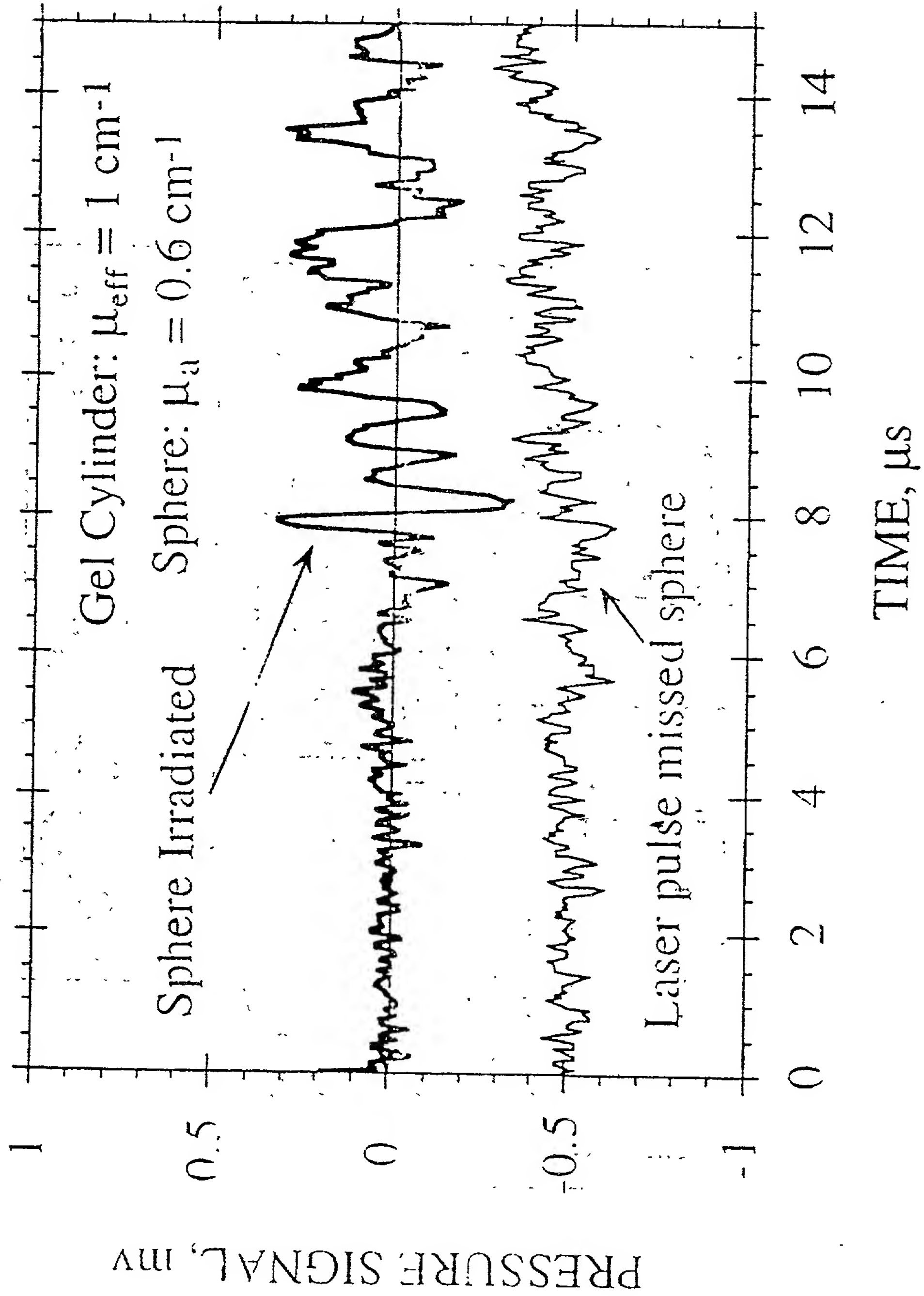


FIGURE 3

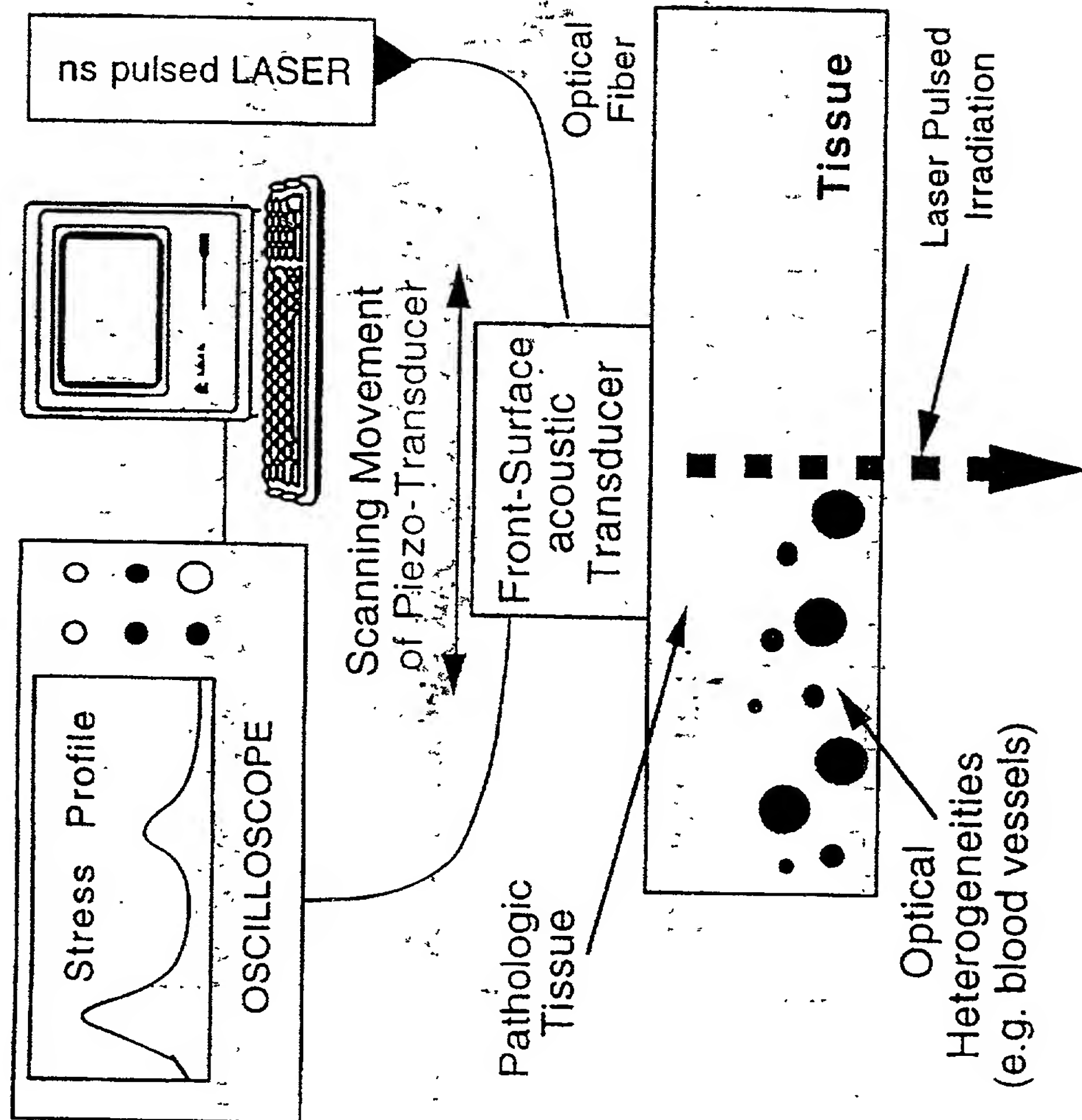


FIGURE 4

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5 / 6

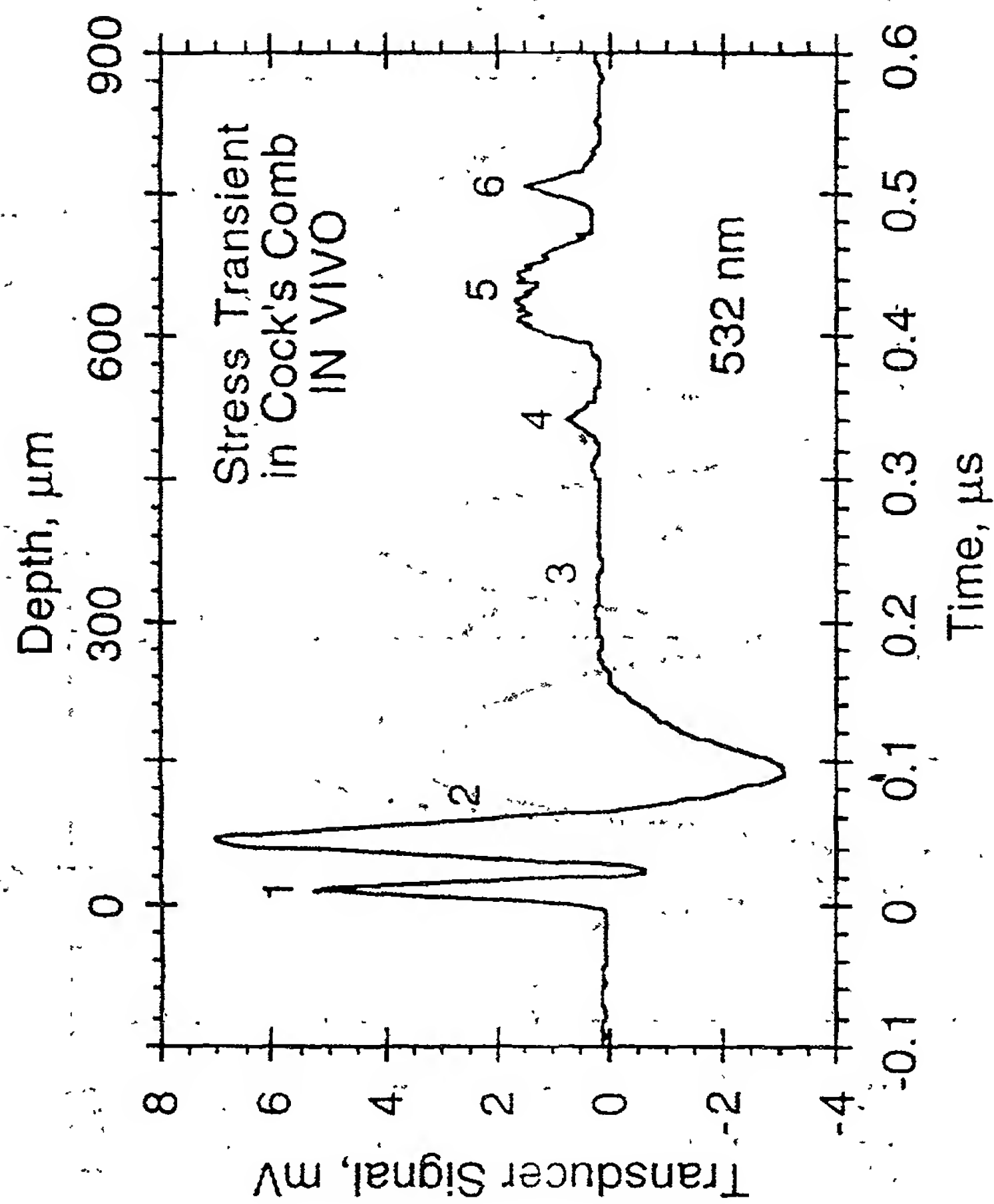


FIGURE 5

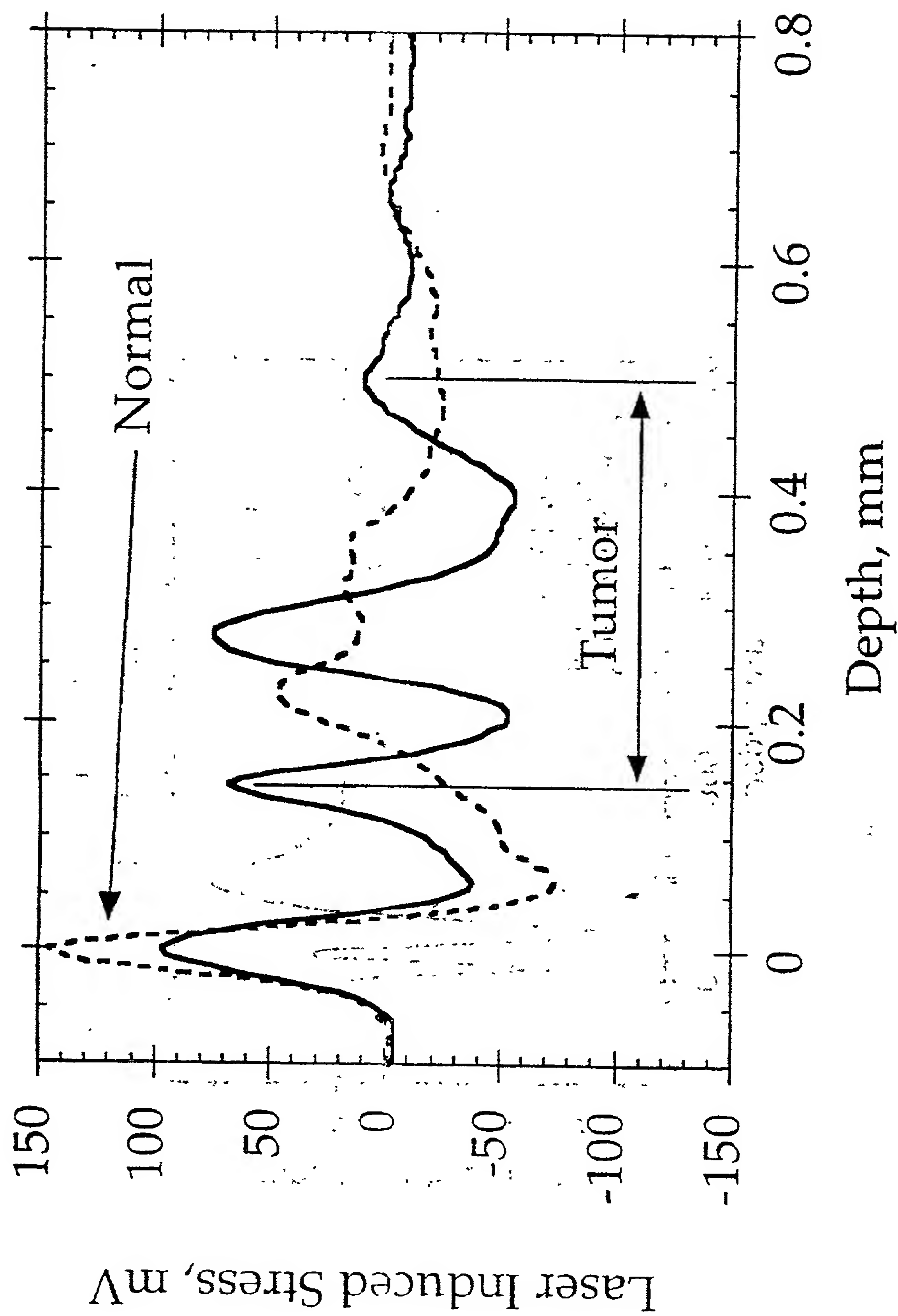


FIGURE 6

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/01815

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : A61B 05/00, 08/13

US CL : 128/653.1

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 128/633, 653.1, 664, 665; 150/340, 341.1, 351; 356/318, 376, 432; 378/21, 22, 64, 86, 87, 901

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 4,710,030 A (TAUC et al) 01 December 1987, Abstract.	1, 2, 4-9, 11-16, 19, 20
Y	US 4,727,420 A (KOHDA et al) 23 February 1988, Abstract	1, 2, 4-9, 11-16, 19, 20
Y, E	US 5,602,894 A (BARDASH) 11 February 1997, Abstract.	2

☒ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:	*T	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
A document defining the general state of the art which is not considered to be of particular relevance	*X*	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
E earlier document published on or after the international filing date	*Y*	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*Z*	document member of the same patent family
O document referring to an oral disclosure, use, exhibition or other means		
P document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search

14 APRIL 1997

Date of mailing of the international search report

07 MAY 1997

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INTERNATIONAL SEARCH REPORT

International application No.
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C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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A61B 17/22, G01S 15/89, H04R 17/00

(52) UK CL (Edition O)

G1G GED G6A G9X
H4J JCX J30X J31J J31P J31V
U1S S1032

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JAPAN, Vol.15, no.337 (C-0862) & JP 31 031 242 A

(58) Field of Search by ISA
INT CL⁵ A61B, G01N

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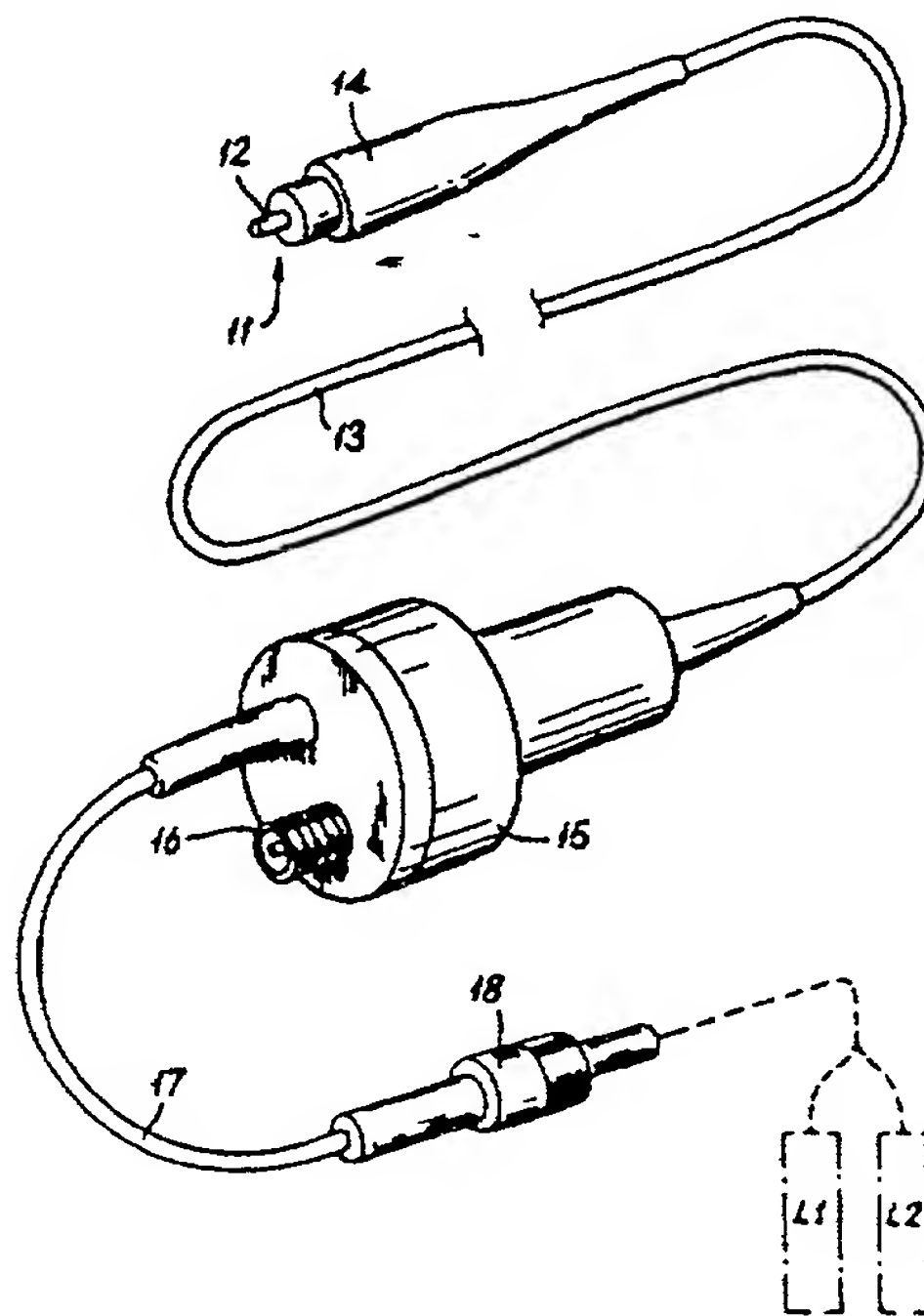
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(54) Laser ultrasound probe and ablator

(57) A laser ultrasound probe, suitable for intravascular use, of the kind having an ultrasonic transducer element comprising an ultrasound receiving surface of piezoelectric polymeric material and an optical fibre with one end directed forwardly from that surface and arranged to receive laser radiation for transmission through the optical fibre and emission from the said one end thereof, wherein the optical fibre is coupled with laser source means adapted to provide alternatively a relatively low average power laser beam, which, when modulated or pulsed and emitted from the one end of the optical fibre and incident on a target, will generate ultrasound at an intensity suitable to be received by the transducer element and converted thereby into electrical monitoring signals, and a relatively high average power laser beam suitable, when incident on the said target, to produce ablation thereof, the transducer element being sufficiently robust to withstand the ultrasound which is then also generated. The relatively low average power laser beam may alternatively be at a first wavelength which, when modulated or pulsed and emitted from the one end of the optical fibre into a medium which is highly absorptive at that wavelength, will cause said medium to generate and propagate ultrasound at an intensity suitable to be reflected by a target contacted by said medium and received by the transducer element and converted thereby into electrical monitoring signals, the relatively high average power laser beam being then at a second wavelength at which the said medium is transmissive and being suitable, when incident on the said target, to produce ablation thereof, the transducing element being sufficiently robust to withstand the ultrasound which is then also generated.



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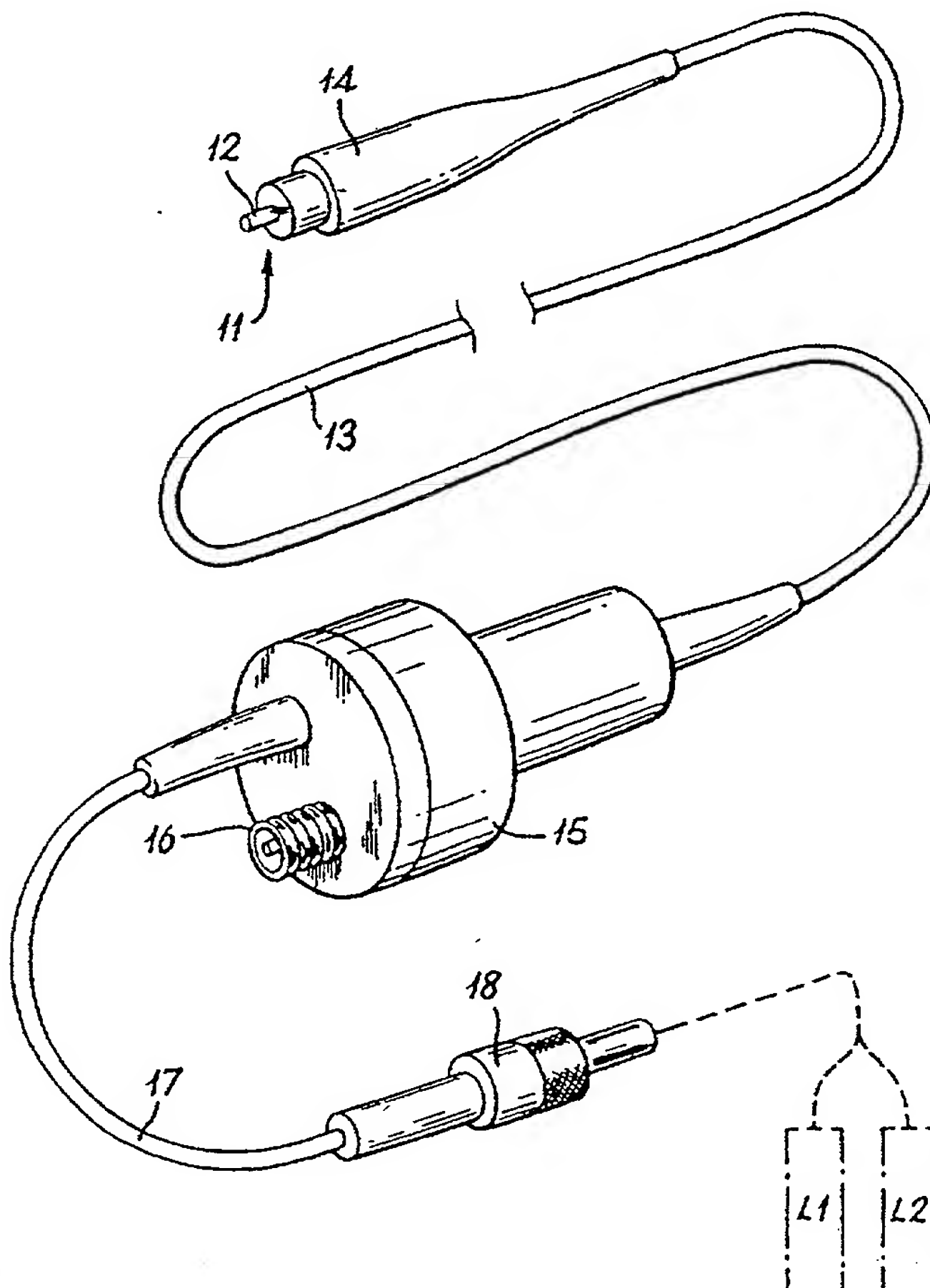
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(54) Title: LASER ULTRASOUND PROBE AND ABLATOR

(57) Abstract

A laser ultrasound probe, suitable for intravascular use, of the kind having an ultrasonic transducer element comprising an ultrasound receiving surface of piezoelectric polymeric material and an optical fibre with one end directed forwardly from that surface and arranged to receive laser radiation for transmission through the optical fibre and emission from the said one end thereof, wherein the optical fibre is coupled with laser source means adapted to provide alternatively a relatively low average power laser beam, which, when modulated or pulsed and emitted from the one end of the optical fibre and incident on a target, will generate ultrasound at an intensity suitable to be received by the transducer element and converted thereby into electrical monitoring signals, and a relatively high average power laser beam suitable, when incident on the said target, to produce ablation thereof, the transducer element being sufficiently robust to withstand the ultrasound which is then also generated. The relatively low average power laser beam may alternatively be at a first wavelength which, when modulated or pulsed and emitted from the one end of the optical fibre into a medium which is highly absorptive at that wavelength, will cause said medium to generate and propagate ultrasound at an intensity suitable to be reflected by a target contacted by said medium and received by the transducer element and converted thereby into electrical monitoring signals, the relatively high average power laser beam being then at a second wavelength at which the said medium is transmissive and being suitable, when incident on the said target, to produce ablation thereof, the transducing element being sufficiently robust to withstand the ultrasound which is then also generated.



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LASER ULTRASOUND PROBE AND ABLATOR

This invention relates to probes comprising a forward-looking ultrasound receiver and optical fibre means for directing laser
5 signals on to a target to generate ultrasound to be sensed by the ultrasound receiver, especially for use in intra-arterial imaging and, preferably, therapy.

It has been proposed, in a paper entitled "Analysis of the acoustic response of vascular tissue irradiated by an ultraviolet
10 laser pulse" by H. Crazzolaro et al. (J. Appl. Phys. 70 (3), 1847-9, 1991), to use an ultrasound probe comprising a disc of a piezoelectric polymer, specifically polyvinylidene fluoride (PVDF), supported on an end of a metal rod element, to monitor the ultrasound generated during ablation of a target by incidence
15 upon it of laser beam pulses emitted from an end of an optical fibre which is physically separate from the ultrasound probe, thereby to distinguish between incidence of the laser pulses on normal arterial wall material and on calcified hard tissue of a sample of arterial material being investigated in vitro.

Probes of the general kind to which the present invention
20 relates have also previously been described, in UK Patent Specification No. 2212920, which describes inter alia such a probe in which the ultrasound receiver comprises a dished circular transducer element of a piezoelectric polymer material
25 such as PVDF and an optical fibre projects coaxially through the centre of the transducer element and has an end, in front of the transducer element, from which laser beam pulses are emitted in use of the apparatus to strike a target, preferably at a focus of the dished transducer element, causing it to emit laser-induced
30 ultrasound signals which are received by the transducer element, thus enabling the target to be investigated ultrasonically.

It is an object of the present invention to provide an improved laser ultrasound probe, suitable for intravascular use, of the kind having an ultrasonic transducer element comprising an
35 ultrasound receiving surface of piezoelectric polymeric material

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and an optical fibre with one end directed forwardly from that surface and arranged to receive laser radiation for transmission through the optical fibre and emission from the said one end thereof.

5 According to one aspect of the invention, the optical fibre of such a probe is coupled with laser source means adapted to provide alternatively a relatively low average power laser beam which, when modulated or pulsed and emitted from the one end of the optical fibre and incident on a target, will generate
10 ultrasound at an intensity suitable to be received by the transducer element and converted thereby into electrical monitoring signals, and a relatively high average power laser beam suitable, when incident on the said target, to produce ablation thereof, the transducer element being sufficiently
15 robust to withstand the ultrasound which is then also generated.

According to another aspect of the invention, the optical fibre of such a probe is coupled with laser source means adapted to provide alternatively a relatively low average power laser beam at a first wavelength which, when modulated or pulsed and
20 emitted from the one end of the optical fibre into a medium which is highly absorptive at that wavelength, will cause said medium to generate and propagate ultrasound at an intensity suitable to be reflected by a target contacted by said medium and received by the transducing element and converted thereby into electrical
25 monitoring signals, and a relatively high average power laser beam at a second wavelength at which the said medium is transmissive and suitable, when incident on the said target, to produce ablation thereof, the transducing element being sufficiently robust to withstand the ultrasound which is then
30 also generated.

In a particular form of this last-mentioned probe in accordance with the invention, the said one end of the optical fibre is directed in a forward longitudinal direction of the probe and the said ultrasonic transducer element is a forward
35 looking transducer element of the probe, susceptible to

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ultrasound generated and propagated forwardly in the said medium and reflected by a first target located in the forward direction, and the probe is further provided with at least one sideways-looking ultrasonic transducer element susceptible to ultrasound generated and propagated in the said medium and reflected by a second target contacted by the medium and disposed laterally of the probe. Preferably such a probe is provided with a plurality, say sixteen, of the sideways-looking transducer elements, disposed circumferentially round the probe and each having its own electrical output-signal connection for connection to signal processing apparatus for image derivation.

In any of the embodiments of the invention as referred to above, the said one end of the optical fibre preferably projects through and forwardly from the said ultrasound receiving surface.

Preferred embodiments of an improved laser ultrasound probe according to the invention are described below with reference to the accompanying drawings, in which:-

Figure 1 is a general perspective view showing a probe according to the invention, together with coupling means for coupling an optical fibre of the probe to laser source means and electrical output connections from a piezoelectric ultrasound transducer of the probe to electrical receiver means (not shown);

Figures 2 and 3 are respectively an elevational view and a longitudinal sectional view, both on a larger scale, of the probe shown in Figure 1;

Figure 4 and 5 are longitudinal sectional views of two further embodiments of a probe according to the invention, incorporating minor constructional modifications of that shown in Figures 2 and 3;

Figure 6 is a phantom perspective view showing an electrical connection of the probe shown in Figure 5;

Figure 7 is a longitudinal sectional view of another probe in accordance with the invention; and

Figure 8 is a cross-section taken on the line VIII-VIII of Figure 7.

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The probe shown in Figure 1 comprises a probe head 11, from a front end face of which projects one end of an optical fibre 12 (which may suitably be a PCS 600 optical fibre), and a cable 13 to which the probe head 11 is secured and through which extend the optical fibre 12 and an electrical connection from the probe head as will be described. The connection between the probe head 11 and the cable 13 may be covered and mechanically strengthened by the provision of a shrunk-on sleeve 14 of suitable plastics material, as shown in Figure 1. At its other end, the cable 13 extends into a signal connector or manifold 15 which includes an electrical socket 16, for example a standard SMC socket, at which the electrical connection from the probe head 11 is terminated. The optical fibre 12 extends continuously through and beyond the manifold 15, and within a protective extension cable covering 17, to an optical fibre connector 18, such as a standard SMA optical fibre connector. By means of the connector 18 the probe head 11 is connected to the output of a laser (not shown) operable selectively at either of two different output levels or (as shown schematically in Figure 1) to the outputs of two lasers L1 and L2 each operable at a respective one of two different output levels. Thus the exposed end of the optical fibre 12 can be made to emit either lower average power pulses of laser light which, on striking a target, generate ultrasonic pulses which impinge on the probe head 14 and are converted into electric signals which appear at the socket 16 for processing in an ultrasonic investigation of the target, or higher average power laser pulses suitable to produce ablation of the target.

The probe head 11 shown in Figure 1, and its connection to the cable 13, are shown on a larger scale and in detail in Figures 2 and 3. The probe head 11, as best seen from Figure 3, comprises a stepped cylindrical shell 20 of perspex or other suitable electrical insulating material, of which the smaller-diameter section is internally threaded to receive a brass or other conductive screw 21 with an axial bore 22 through

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which the optical fibre 12 extends. The interior of the larger-diameter section of the shell 20 is filled with a silver-loaded epoxy resin plug 23 (through which the optical fibre 12 also extends axially). The plug 23 and the surrounding edge of the shell 20 provide a support for a piezoelectric transducer element in the form of a superposed film 24 of a piezoelectric polymer, suitably PVDF, provided with a metallised surface film 25 on its surface remote from the plug 23. The piezoelectric film 24 is bonded with a suitable adhesive, for example cyanoacrylate, to the plug 23 and to the annular and of the shell 20 which ensures electrical isolation of the plug 23 from the metallised film 25. The film 25 is covered by a finishing surface layer 26 of silver conductive paint which also covers the outer surface of the shell 20.

15 The cable 13 has at its centre the optical fibre 12 and also includes an inner electrical conductor in the form of an enamelled copper wire 27 of which one end, stripped of its insulating enamel, is wrapped around the threads of the screw 21 where it is held in place by means of a shrunk-on heat-shrink sleeve 28. The cable 13 also includes an outer screening conductor formed by a braided copper sheath 29, and one end of this is secured by means of silver-loaded epoxy resin 30 to the conductive paint coating 26 of the shell 20.

20 Thus one surface of the PVDF film 24 is electrically connected by its metallic film layer 25, the conductive paint layer 26 (which also serves as an extension of the external screening) and the silver-loaded epoxy bond 30 to the outer conductor 29 of the cable, while the other surface of the film 24 is in contact with the silver-loaded epoxy plug 23 and is electrically connected through it and the screw 21 to the cable inner conductor 27; and the inner and outer conductors of the cable are connected respectively to the inner and outer contacts of the socket 16.

35 The probe heads shown in Figures 4, 5 and 6, are similar to that shown in Figures 2 and 3, and corresponding parts are

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indicated by the same reference numerals. In the probe head shown in Figure 4, however, the inner conductor 27 is bonded and electrically connected directly to the silver-loaded conductive epoxy plug 23, by means of a further added small body of silver-loaded conductive epoxy resin 21a, the conductive screw 21 of the head shown in Figure 3 being omitted. In the head shown in Figures 5 and 6, the inner conductor 27 is conductively secured to one end of a copper wire conductor 21b by means of solder 21c, the other end of the conductor 21b being formed as a loop embedded in the silver-loaded epoxy plug 23 (as best seen in Figure 6) and in good electrical connection therewith. In this case a shrunk-on heat-shrink sleeve 28 protects the soldered connection between the conductors 27 and 21b and provides insulation from the outer conductive sheath 29.

The above-described embodiments of the invention provide robust and constructionally simple forward-looking probe heads for use in investigating (and preferably also ablating) arterial blockages. Any of the above-described probe heads according to the invention may without difficulty be made with an outside diameter no greater than 3mm, which is probably as small as will be required for medical purposes since such a probe may be used to investigate and ablate blockages in correspondingly small arterial vessels, and smaller vessels, if they become blocked, become bypassed in any event.

The use of piezoelectric polymeric material, in particular PVDF, rather than a piezoelectric ceramic, as the ultrasonic transducer is preferred for several reasons. Firstly, PVDF provides a much better acoustic impedance match with body tissue or fluid than does a ceramic, and is a much better receiver of ultrasonic signals. Also, PVDF is inherently wideband in its frequency response because of its higher internal losses compared with piezoelectric ceramic materials, thereby tending to reduce the amount of ultrasonic wave reverberation within the transducer material and thereby tending to increase the resolution of the transducer. Furthermore, PVDF is robust rather than brittle, and

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is therefore well able to withstand ultrasound generated during high-power use of the probe to effect tissue ablation.

It will be understood that although in the illustrated probe heads the PVDF film 24 is metallised on only one surface, with reliance being placed on good all-over contact of its other surface with the conductive epoxy resin plug 23, this other surface of the film may also be metallised if desired to remove the necessity of good all-over contact (so long as care is taken to avoid short-circuiting to the film 25 or the paint layer 26). Also, instead of applying a pre-formed film 24, the film-form transducer element may be formed in situ by applying to the end of the plug 23 a solution of the PVDF polymer in a suitable solvent, spinning the device to remove excess, and heat-treating and subsequently poling the coated polymer layer to render it piezoelectrically active.

It will also be understood that although the PVDF film 24, which may be some 10µm in thickness, is shown as being flat it may be slightly dished (for example by slightly dishing the supporting end of the epoxy plug 23) in order to provide a focussing effect. Alternatively, as is described in UK Patent Specification No. 2212920, already referred to, a focusing effect may be obtained by dividing the PVDF film into electrically separate annular zones each of which generates its own signal, with due account being taken of phase differences between the signals; but, as will be recognised, this requires a separate electrical connection for each of the annular zones and would necessitate some redesign of the probe heads to provide such multiple connections.

For carrying out an ultrasonic examination by means of a probe according to the invention, the optical fibre in the cable 17 is fed via the connector 18 from a suitable laser source, which may conveniently be a conventional Q-switched Nd:YAG laser emitting pulses of 20 ns duration at a repetition frequency of, say, 50 Hz and a laser wavelength of 1.06µm focused by a lens of, say, 4 cm focal length into one end of an optical

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fibre of which the other end is connected through the connector 18 to the optical fibre in the cable 17 and thus to the optical fibre 12. The output of the laser may be attenuated by the use of neutral density filters to such a level that the energy delivered by each laser pulse emitted from the exposed end of the optical fibre 12 is about 3 mJ. Pulses of this energy have been demonstrated as being quite adequate to excite a target surface into ultrasonic oscillation which is easily detectable by a transducer of the kind constituted by the PVDF film 12. The resulting electrical signals provided by the probe head 11 are processed in known manner to provide ultrasonic imaging.

The same laser may be re-adjusted to provide a higher-energy output suitable for ablating the target, for example by switching the laser to operate in a normal mode instead of a Q-switch mode.

It will, however, be understood that alternative low and high laser energy levels may be achieved in other ways. At the target surface, the important parameter is power per unit area, and this can be varied by de-focussing the spot illuminated by the laser, either by altering the distance of the end of the optical fibre from the target surface, and/or by altering the optical system by which the laser output beam is fed to the optical fibre system. Alternatively, as indicated schematically in Figure 1, the different laser power levels may be derived from two different lasers L1 and L2, possibly operating at different wavelengths, connected to respective optical fibre transmission systems which merge before reaching their common connection to the connector 18.

Figures 7 and 8 illustrate a more elaborate probe head according to the invention which includes not only a forward-looking ultrasound receiving transducer element but also a plurality of sideways-looking transducer elements, all intended to receive ultrasound generated by a laser beam transmitted down an axial optical fibre 12. The probe head, indicated generally by the reference numeral 31, has an electrically conductive metallic central microtube 32 through which the optical fibre 12 extends, and surrounding the microtube 32 are an electrically

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conductive metal disc electrode 33 in electrical connection with it and an electrically insulating body 34, suitably of epoxy resin, along the outer periphery of which extend, in the axial direction, a plurality of electrodes 35. As shown in Figure 8, the electrodes 35, which may be sixteen in number, are regularly distributed round the cylindrical periphery of the body 34. Each is spaced, and electrically insulated, at one end from the electrode 33, and at its other end terminates in a terminal section 36 which extends on an end face of the body 34. The electrodes 35 and their terminal sections 36, and also the electrode 33, may be preformed metal elements which are assembled in their intended positions relative to the microtube 32 prior to casting the epoxy resin body 34 between them, or they may be thin metallic films which are deposited by any convenient method on the body 34 after it has been formed.

The electrode 33, and the cylindrical peripheral surface of the body 34 and the associated electrodes 35, are coated with a continuous layer 37 of suitable piezoelectric polymer such as PVDF. As described above, this may be applied by a spin coating process in which PVDF is applied in a suitable solvent, the epoxy resin body 34 is rotated to obtain an even distribution of the applied layer, and the layer is then dried, heat treated and poled to render it piezoelectrically active.

A terminal cap 38 is secured by means of a suitable adhesive to that end of the body 34 which is provided with the electrode terminations 36. The cap 38 is formed with a plurality of bores 39, each in register with a respective termination 36, for receiving a respective terminal wire 40 to connect electrically with the termination 36. The bores 39 are of enlarged diameter at their ends adjacent the terminations 36, so that a small quantity of electrically conductive silver-loaded epoxy resin 41 inserted through each bore before fitting of the respective wire 40 may be forced by insertion of the wire into good contact both with the wire and with the adjacent termination 36. The cap 38 has a further bore, 42, which accommodates a further

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terminal wire, 43, which is electrically connected, by solder or silver-loaded epoxy resin 44, to the microtube 32 and thus to the electrode 33.

Finally, the outer surface of the PVDF layer 37 is covered with a layer of silver-loaded electrically conductive paint 45, which also extends over the outer surface of the cap 38. It will be understood that, for use, the probe head 31 is secured on the end of a cable which (like the cable 13 described above) has the optical fibre 12 extending through it and has an electrically conductive outer sheath to which the conductive paint layer 45 is connected so as to constitute an extension of the electrical shielding provided by the cable sheath. In this case, the cable also includes seventeen signal conductor wires, of which one is connected to the terminal wire 43 and each of the others is connected to a respective one of the terminal wires 40, the signal conductor wires being enamelled or otherwise insulated from one another and connected at their other ends to respective pins of a multi-pin socket corresponding to the socket 16 shown in Figure 1.

20 The layer 37 of piezoelectric polymeric material in the probe head 31 is continuous over the electrode 33 and all the electrodes 35, but each of its regions covering one of these electrodes, and sandwiched between that electrode and the overlying outer paint layer 45, constitutes an effectively
25 separate ultrasonic transducer element, with substantially no cross-talk from one transducer element to another. It will be appreciated that although for purposes of illustration the layer 37 is shown as having substantial thickness, in practice its thickness may be only some 10 μm or less and lateral
30 transmission of ultrasonic vibration (which in any case is quite heavily damped) is minimal. Thus the probe head 31 incorporates a forward-looking ultrasonic transducer element producing electrical output signals at the terminal wire 43, and a ring of sideways-looking transducer elements each producing electrical
35 output signals at a respective one of the terminal wires 40.

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These transducer output signals, applied in a known manner to appropriate signal processing equipment, enable an ultrasonic image of the surroundings of the probe head 31, both around and ahead of it, to be obtained.

5 As in the case of the probe head 11 shown in Figures 1 to 3, the optical fibre 12 of the probe head 31 is connected to receive and transmit a second laser beam of relatively higher average power sufficient to provide ablation of a target disposed ahead of the exposed end of the optical fibre 12, as well as a first laser beam of lower average power sufficient to generate ultrasound by means of which the target can first be investigated ultrasonically. As described above with reference to the probe head 11 shown in Figures 1 to 3, the ultrasound may be generated in the target itself by impingement of the first laser beam upon it, and in that case the ultrasound from the target impinges directly on the forward-looking transducer element constituted by the part of the layer 37 overlying the electrode 33 and indirectly, after reflection at any reflective boundary disposed laterally of the probe head, by any appropriate one or more of the sideways-looking transducer elements constituted by parts of the layer 37 overlying electrodes 35.

However, it is preferred, in the case of a probe provided with sideways-looking transducer elements as shown in Figures 7 and 8, to arrange that the source of the ultrasound shall be not the ultimate target for ablation but the medium immediately in front of the free end of the optical fibre 12. It is already established practice, when a probe of this kind is advanced along a blood vessel, to inject water or saline solution into the vessel so as to displace blood from the part of the vessel around and ahead of the probe head. If, as the laser L1 of Figure 1, there is used an Er:YAG laser operating at a wavelength of 2.94 μm , at which water and saline solution are highly absorptive, suitable laser pulses from that laser emitted from the exposed end of the optical fibre 12 into the water or saline solution ahead of the fibre end are absorbed within a very short

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distance and generate ultrasound which is radiated laterally as well as forwards so as to be reflected by the vessel walls laterally of the probe head as well as by any obstruction or constriction ahead; so that both the sideways-looking and the forward-looking transducer elements produce electrical output signals which, after processing, provide an ultrasonically derived image of the vessel around and ahead of the probe head. This image may be used for positioning the probe head relative to the vessel walls and an obstruction ahead, before switching to the second laser L2 to provide a second laser beam at a wavelength for which the water or saline medium is transmissive and at a power level suitable for ablating the obstruction. It will be understood that although this choice of a suitable combination of laser wavelength and absorptive medium, to provide an essentially pulse-echo type of laser-generated ultrasonic probe, is especially preferred in the case of a probe with sideways-looking ultrasonic transducer elements (since it provides a well defined ultrasound source, in the medium immediately ahead of the probe, instead of a source at a variable distance ahead), it may also be employed in use of a probe which, like that shown in Figures 2 and 3, is only forward-looking.

Probes in accordance with the invention may, and preferably do, incorporate, in known manner, means for co-operating with guide wires to assist in steering the probe head along an artery; but, for simplicity and clarity of the disclosure of the invention, no such means or wires are illustrated in the accompanying drawings.

It will be appreciated that since, in a probe according to the invention, the ultrasonic signals are generated by laser irradiation, an ultrasonic transducer element in such a probe is required only to receive, and not to generate, ultrasound. Piezoelectric polymers are ideal materials for use to form the transducer elements in such a situation, since they have high "receive" sensitivity and, compared with conventional piezoelectric ceramic materials, are chemically more stable,

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mechanically more robust and acoustically better matched to water and blood. Due to their low dielectric permittivity, they have a large dielectric constant, making them good ultrasonic receivers; furthermore, because of their high internal dielectric and mechanical losses, reception is intrinsically wide band.

It may be desirable that the laser L1, providing for the ultrasonic investigation, should be tunable over a range of laser wavelengths. In that case, this laser may be constituted by an optical parametric oscillator, offering a wide range of tunability (from about 2 μm to 200 nm) and a wide range of laser pulse wavelengths. By such means, good discrimination may be obtained between healthy and diseased tissue; for example, at a wavelength of 308 nm, optical penetration depth in tissue is approximately 0.15 mm, permitting an ultrasound centre frequency of the order of 15 MHz, which may prove to be close to the optimum for laser probing. If it transpires that such is the case and a fixed laser wavelength of 308 nm is satisfactory, a compact XeCl excimer laser may be used instead as the laser source.

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CLAIMS

1. A laser ultrasound probe, suitable for intravascular use, of the kind having an ultrasonic transducer element comprising an ultrasound receiving surface of piezoelectric polymeric material and an optical fibre with one end directed forwardly from that surface and arranged to receive laser radiation for transmission through the optical fibre and emission from the said one end thereof, characterised in that the optical fibre is coupled with laser source means adapted to provide alternatively a relatively low average power laser beam, which, when modulated or pulsed and emitted from the one end of the optical fibre and incident on a target, will generate ultrasound at an intensity suitable to be received by the transducer element and converted thereby into electrical monitoring signals, and a relatively high average power laser beam suitable, when incident on the said target, to produce ablation thereof, the transducer element being sufficiently robust to withstand the ultrasound which is then also generated.
2. A laser ultrasound probe, suitable for intravascular use, of the kind having an ultrasonic transducer element comprising an ultrasound receiving surface of piezoelectric polymeric material and an optical fibre with one end directed forwardly from that surface and arranged to receive laser radiation for transmission through the optical fibre and emission from the said one end thereof, characterised in that the optical fibre is coupled with laser source means adapted to provide alternatively a relatively low average power laser beam at a first wavelength which, when modulated or pulsed and emitted from the one end of the optical fibre into a medium which is highly absorptive at that wavelength, will cause said medium to generate and propagate ultrasound at an intensity suitable to be reflected by a target contacted by said medium and received by the transducing element and converted thereby into electrical monitoring signals, and a relatively high average power laser beam at a second wavelength at which the said medium is transmissive and suitable, when

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incident on the said target, to produce ablation thereof, the transducing element being sufficiently robust to withstand the ultrasound which is then also generated.

3. A laser ultrasound probe as claimed in Claim 1 or Claim 2, characterised in that the said one end of the optical fibre projects through and forwardly from the said ultrasound receiving surface.

4. A laser ultrasound probe as claimed in Claim 2, characterised in that the said one end of the optical fibre is directed in a forward longitudinal direction of the probe and the said ultrasonic transducer element is a forward-looking transducer element of the probe, susceptible to ultrasound generated and propagated forwardly in the said medium and reflected by a first target located in the forward direction, and the probe is further provided with at least one sideways-looking ultrasonic transducer element susceptible to ultrasound generated and propagated in the said medium and reflected by a second target contacted by the medium and disposed laterally of the probe.

5. A laser ultrasound probe as claimed in Claim 4 and provided with a plurality, suitably sixteen, of the sideways-looking transducer elements, disposed circumferentially round the probe and each having its own electrical output-signal connection for connection to signal processing apparatus for image derivation.

6. A laser ultrasound probe substantially as described herein with reference to any of the accompanying drawings.

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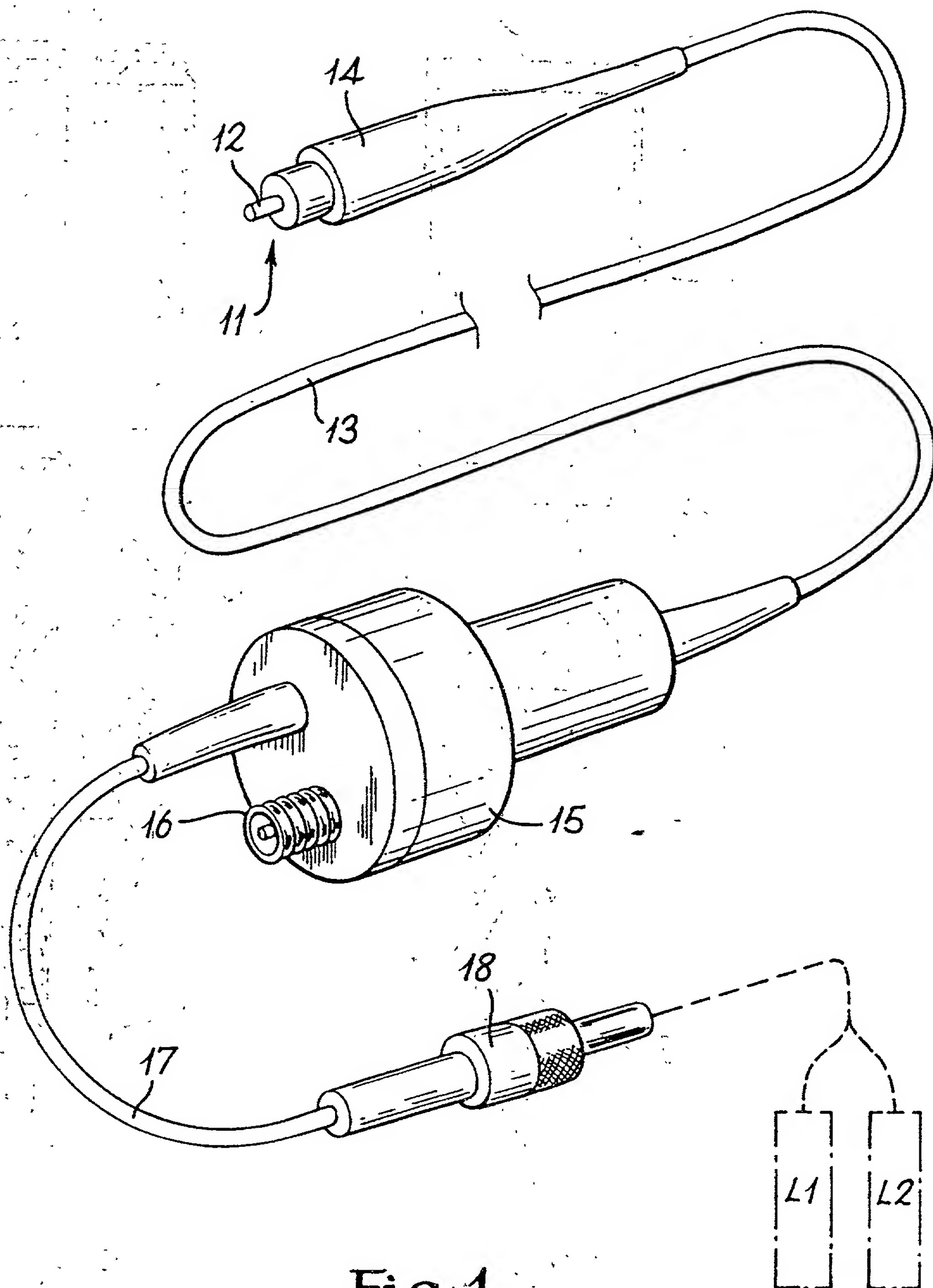


Fig. 1

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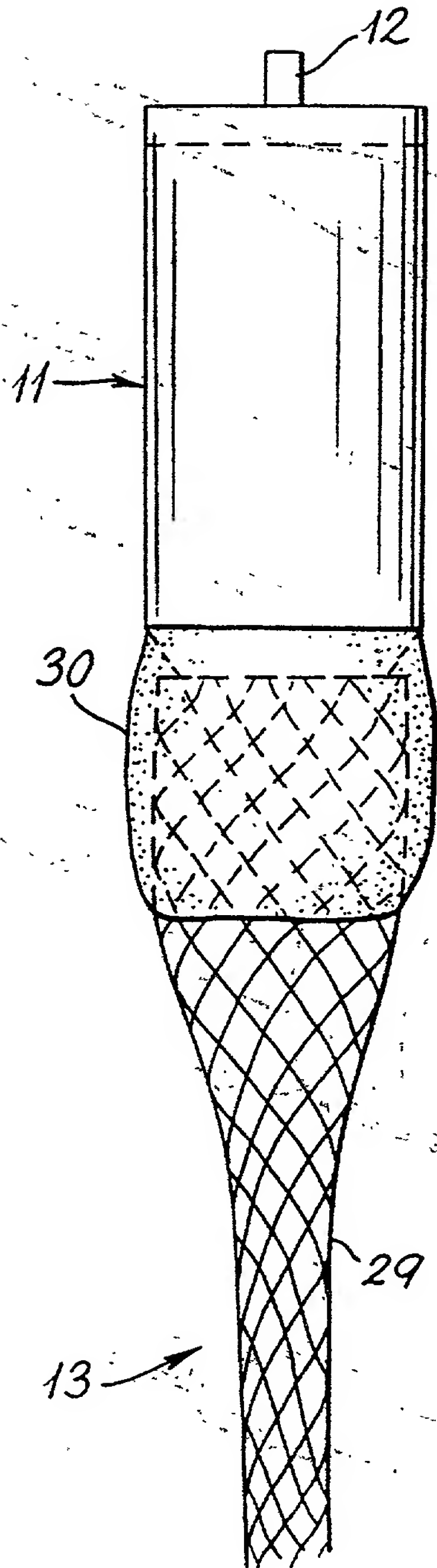


Fig. 2

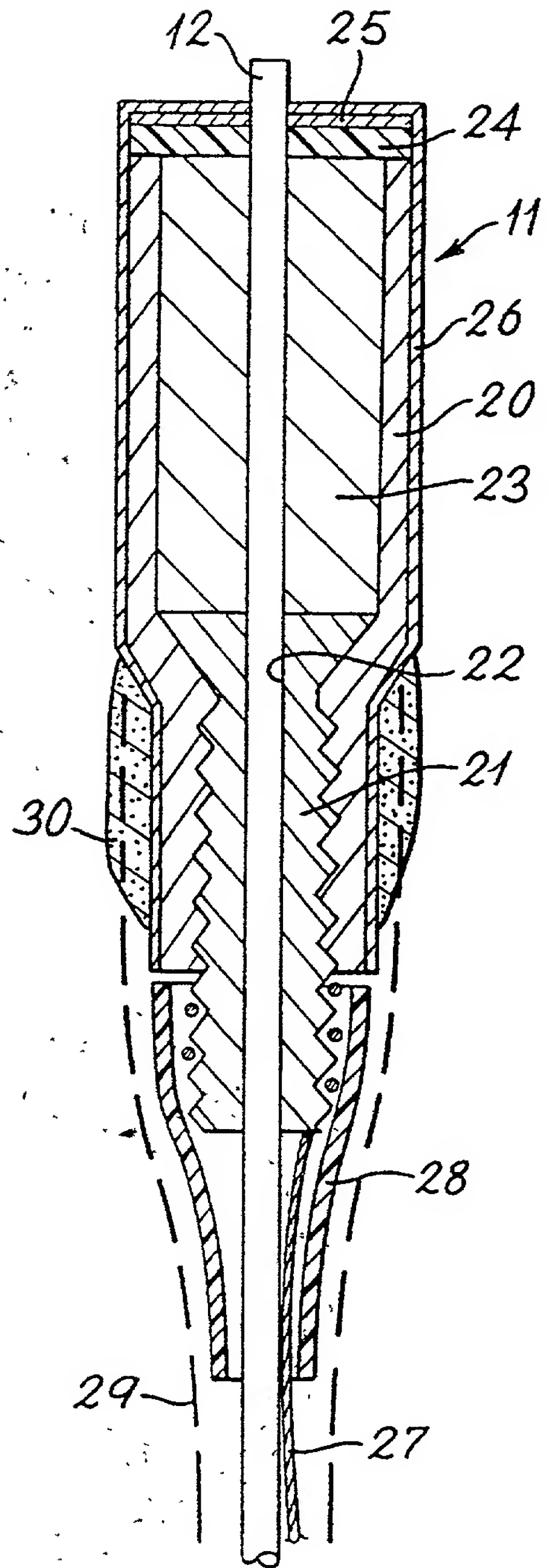


Fig. 3

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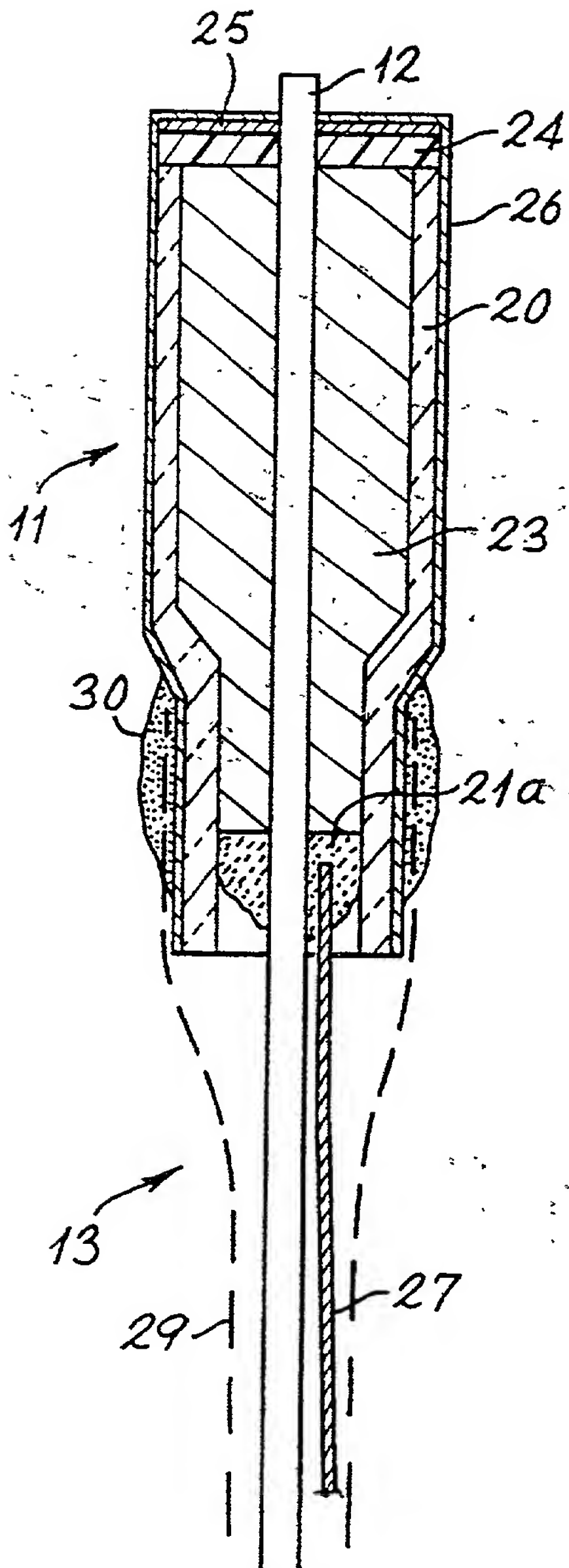


Fig. 4

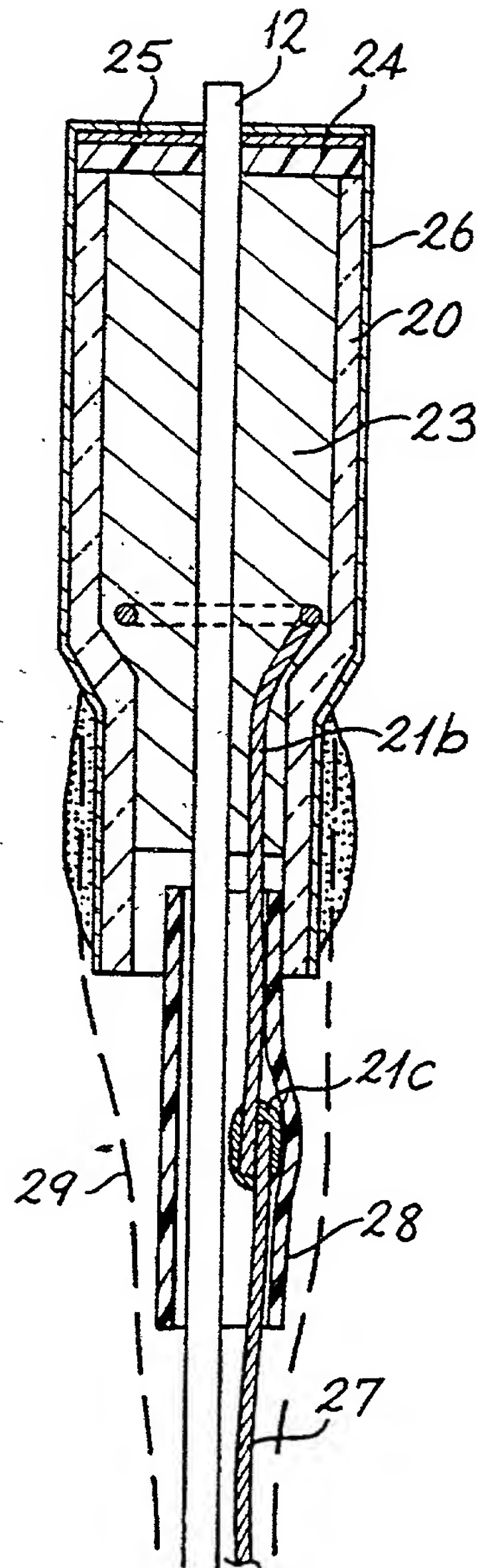


Fig. 5

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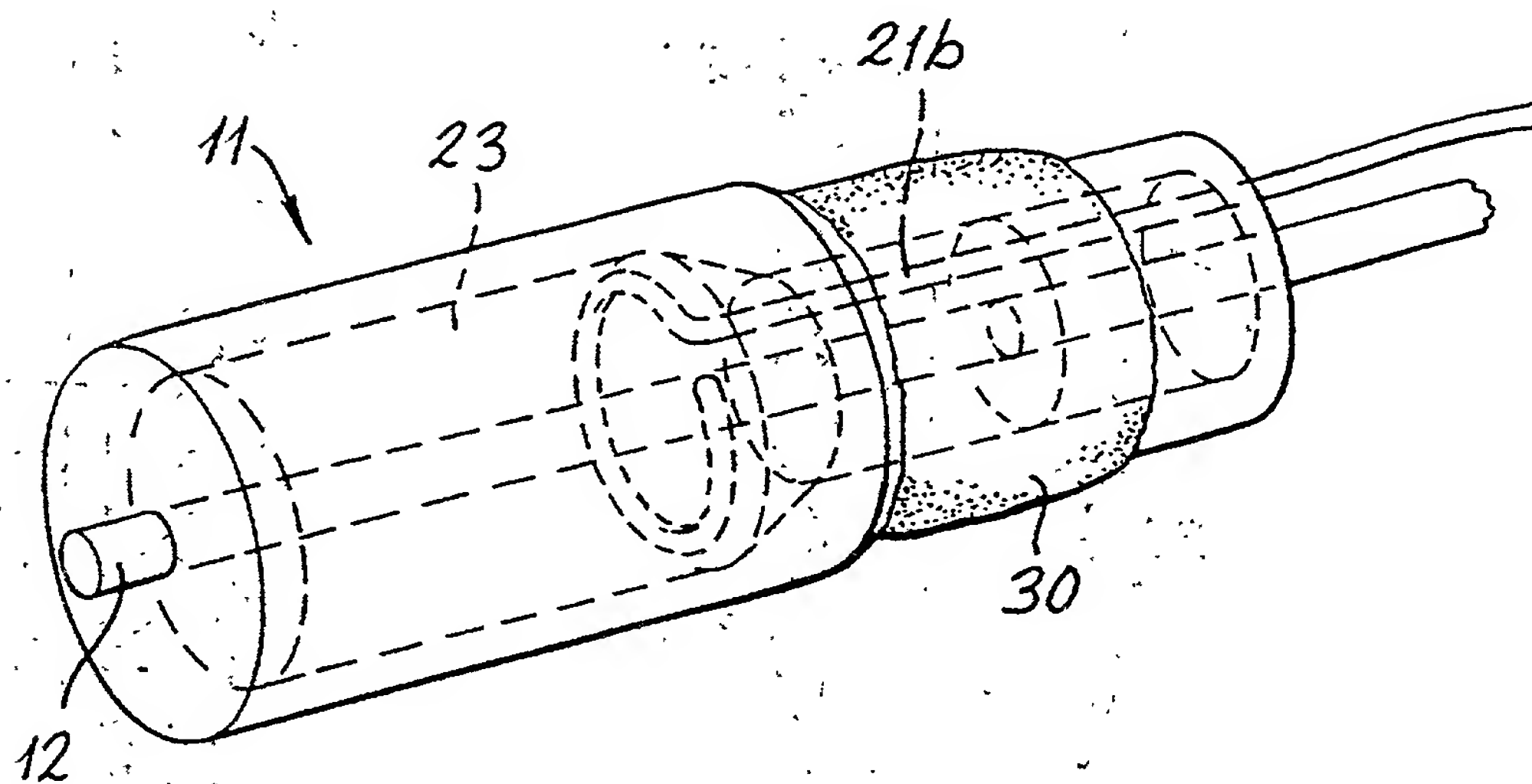


Fig. 6

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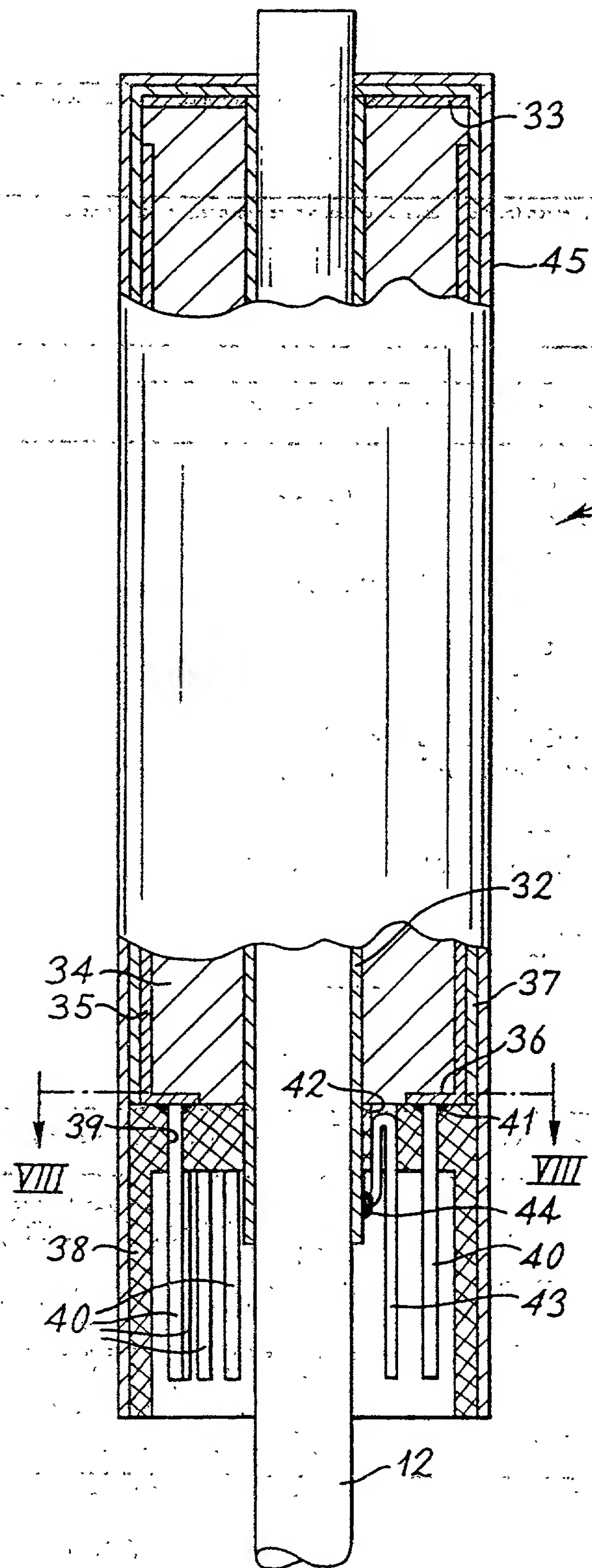


Fig. 7

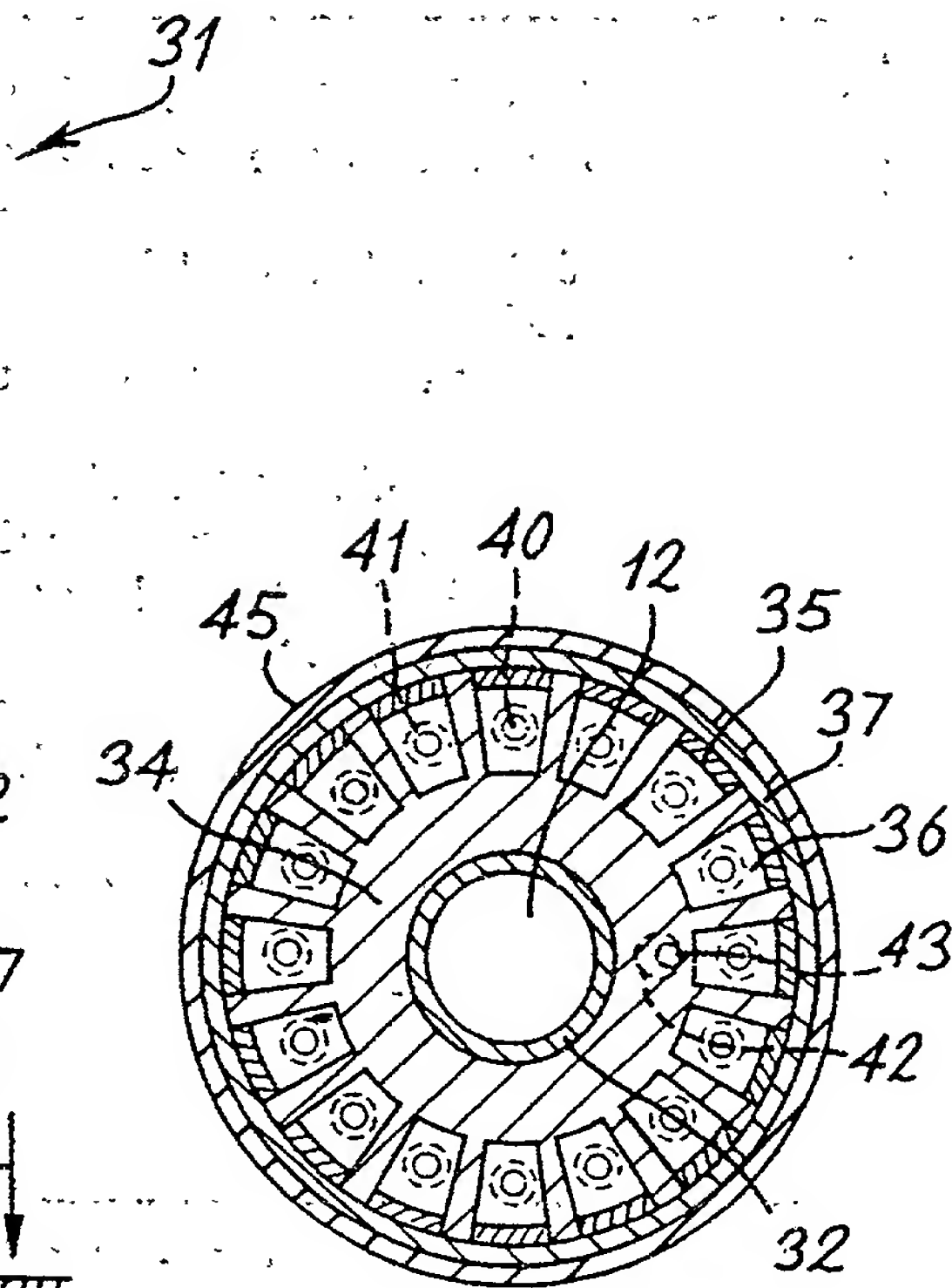


Fig. 8

A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 A61B17/22

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 5 A61B G01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO,A,92 07623 (C.R.BARD INC.) 14 May 1992 see the whole document	1,3
Y	WO,A,92 16140 (WINSTON T.R.) 1 October 1992 see the whole document	1-5
Y	PATENT ABSTRACTS OF JAPAN vol. 15, no. 252 (C-0844) 26 June 1991 & JP,A,30 082 482 (OLYMPUS OPTICAL CO.) see abstract	1-5
A	EP,A,0 329 492 (ANGELSEN ET AL.) 23 August 1989 see abstract; figures	1-5



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents :

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Date of the actual completion of the international search

18 August 1994

Date of mailing of the international search report

23.09.94

Name and mailing address of the ISA

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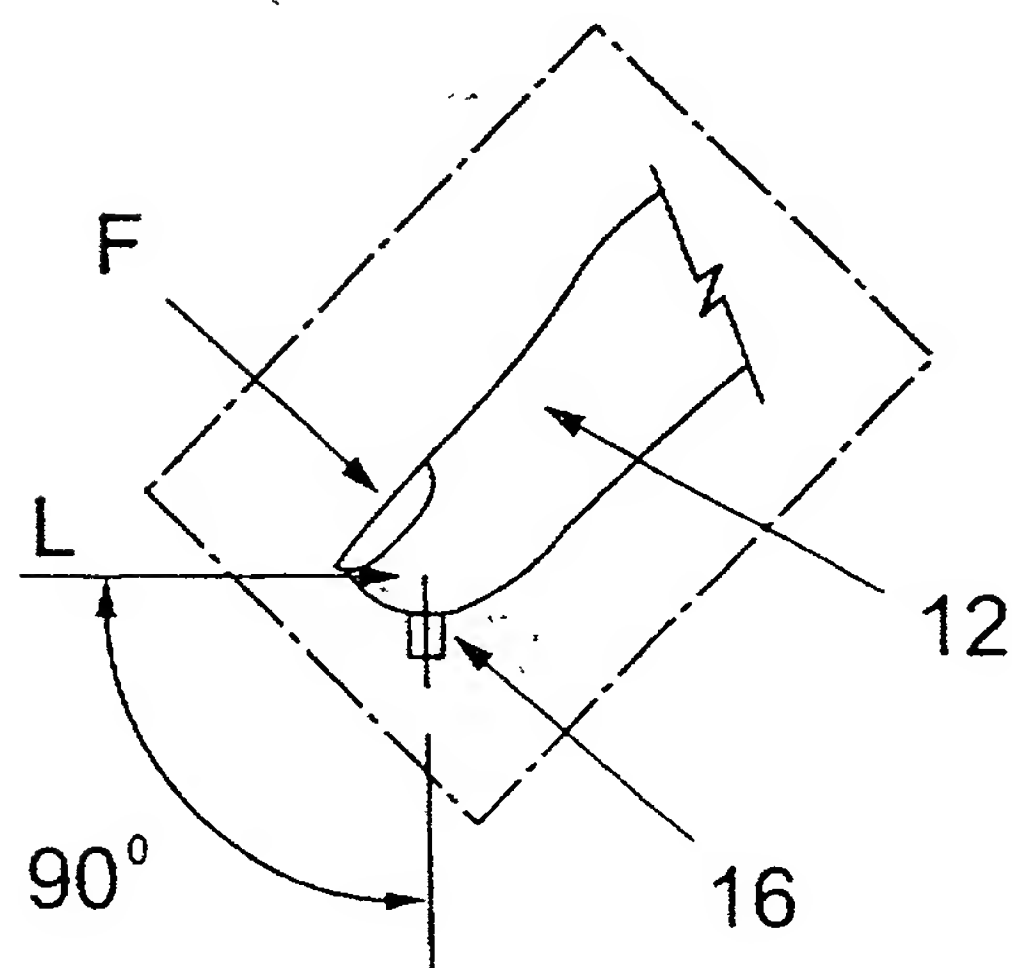
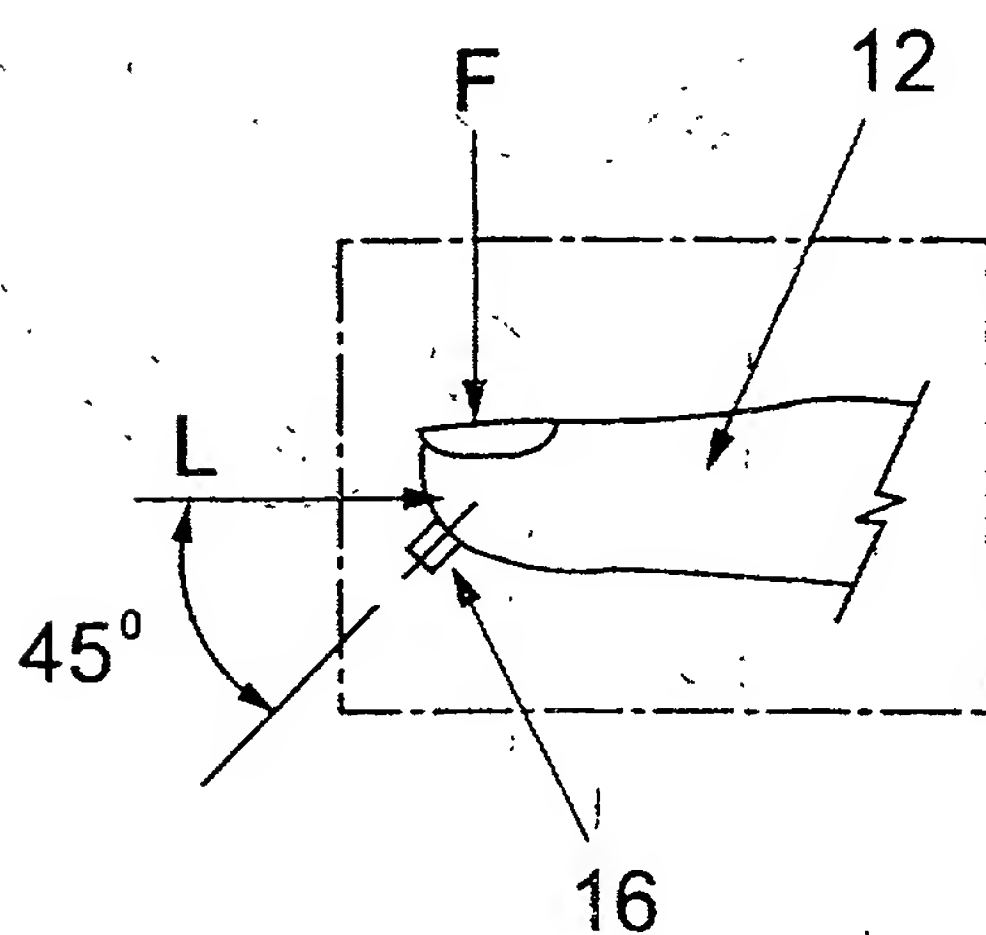
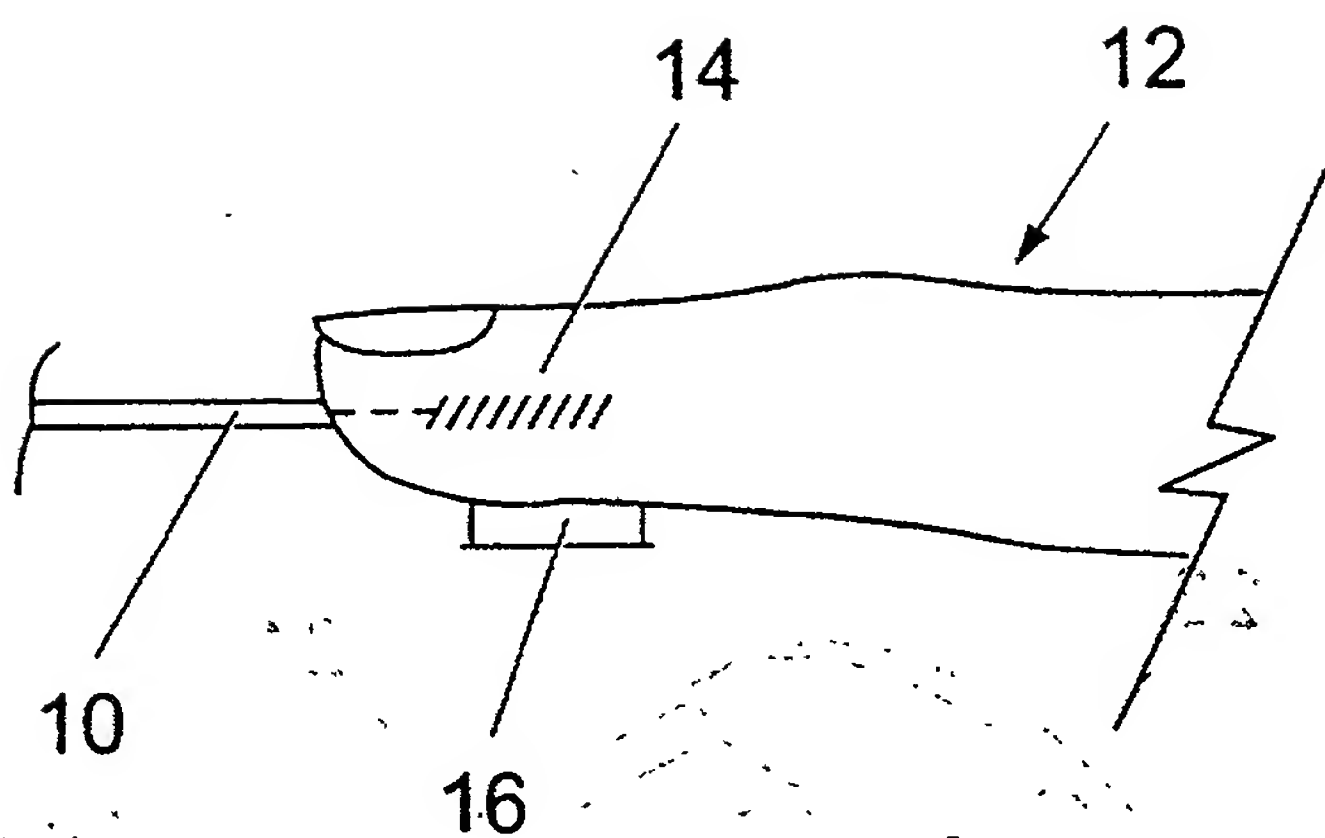
Kouzelis, D

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US,A,5 163 432 (UENO ET AL.) 17 November 1992 see the whole document	1,3
A	PATENT ABSTRACTS OF JAPAN vol. 15, no. 337 (C-0862) 27 August 1991 & JP,A,31 031 242 (OLYMPUS OPTICAL CO.) see abstract	1

100194 0000

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A-9207623	14-05-92	US-A- 5254112	19-10-93
		AU-A- 8946191	26-05-92
WO-A-9216140	01-10-92	AU-A- 1924192	21-10-92
		EP-A- 0576607	05-01-94
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		JP-A- 2005936	10-01-90
US-A-5163432	17-11-92	JP-A- 4075651	10-03-92
		JP-A- 4135555	11-05-92



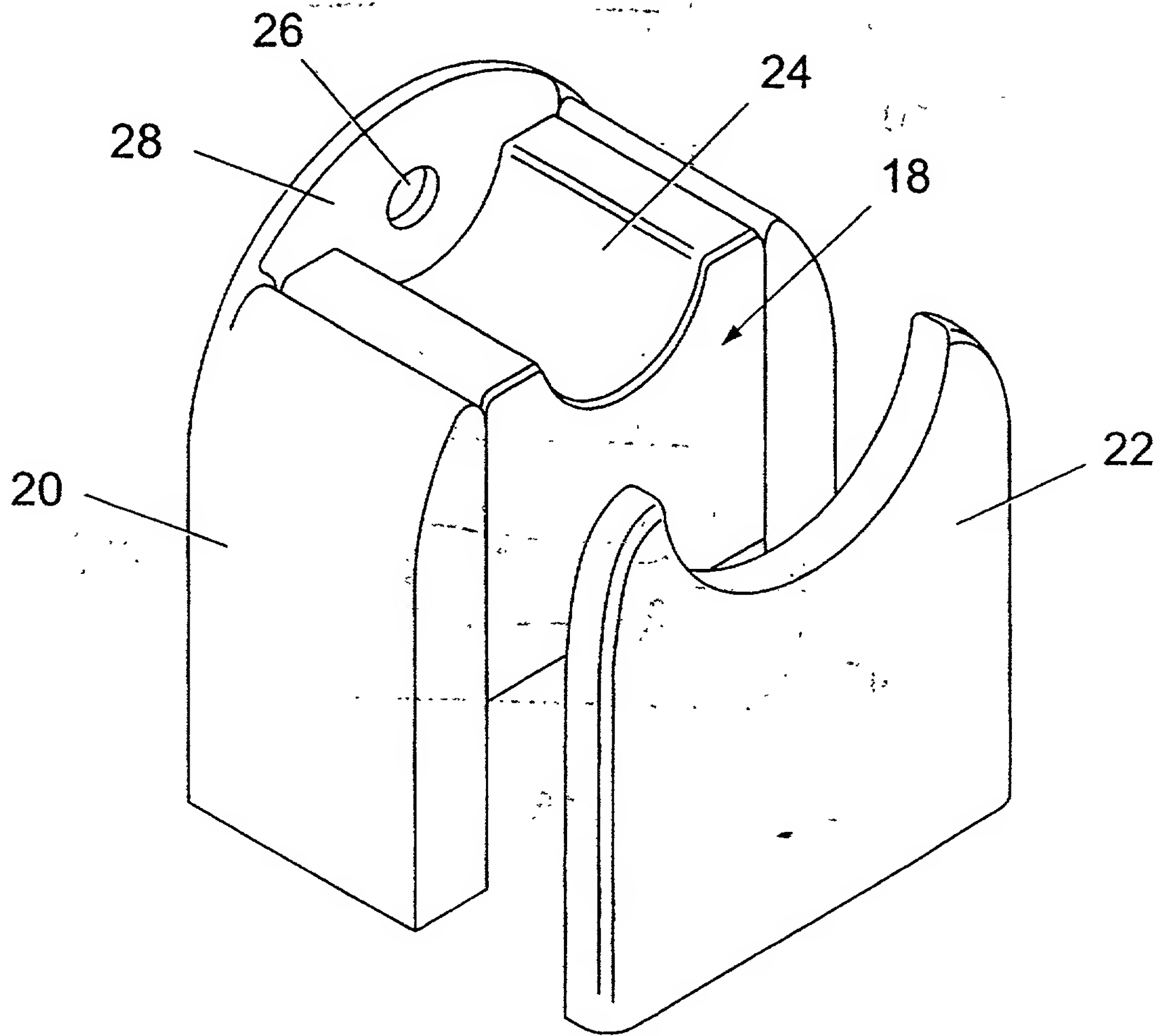


Fig. 2

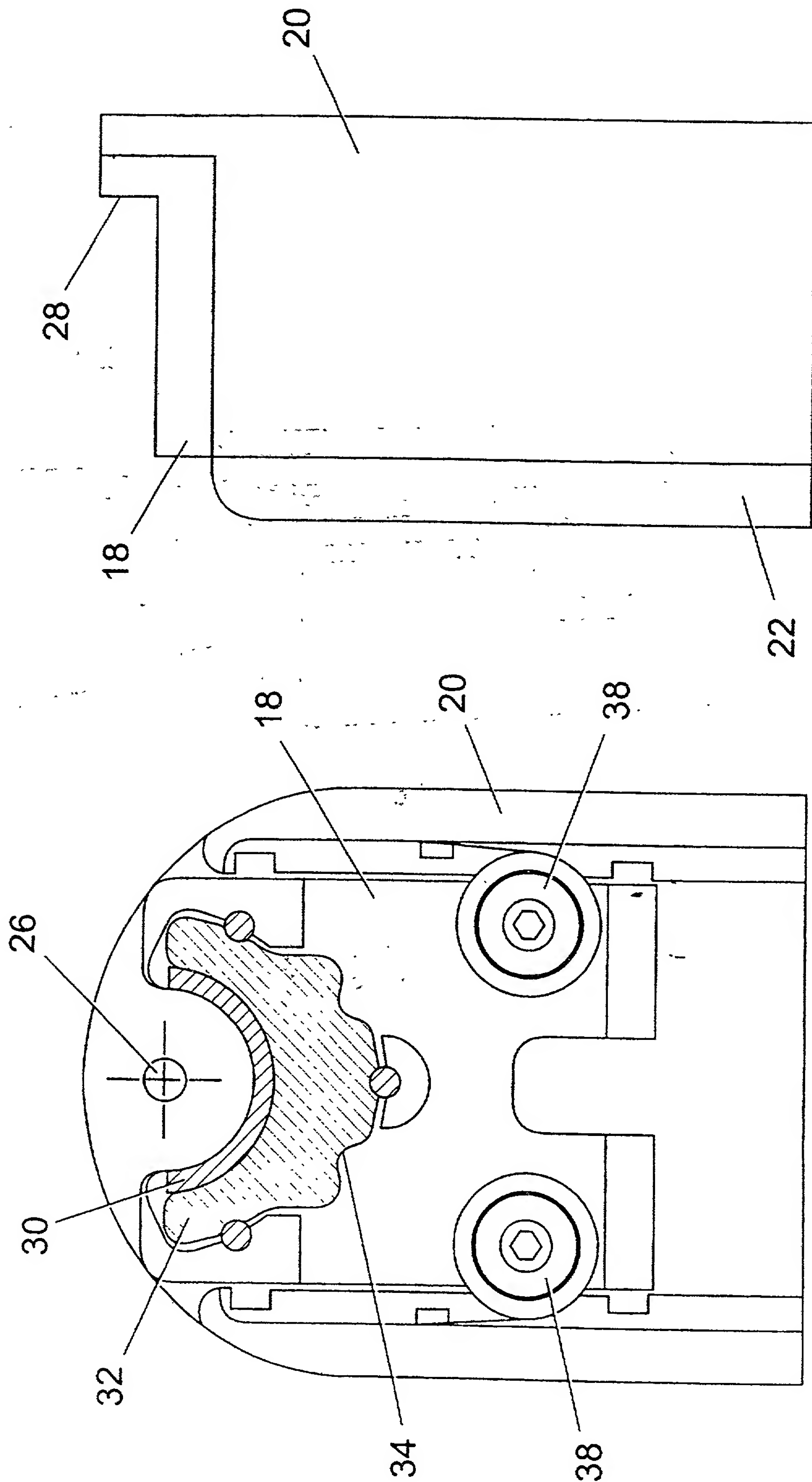


Fig. 4

Fig. 3

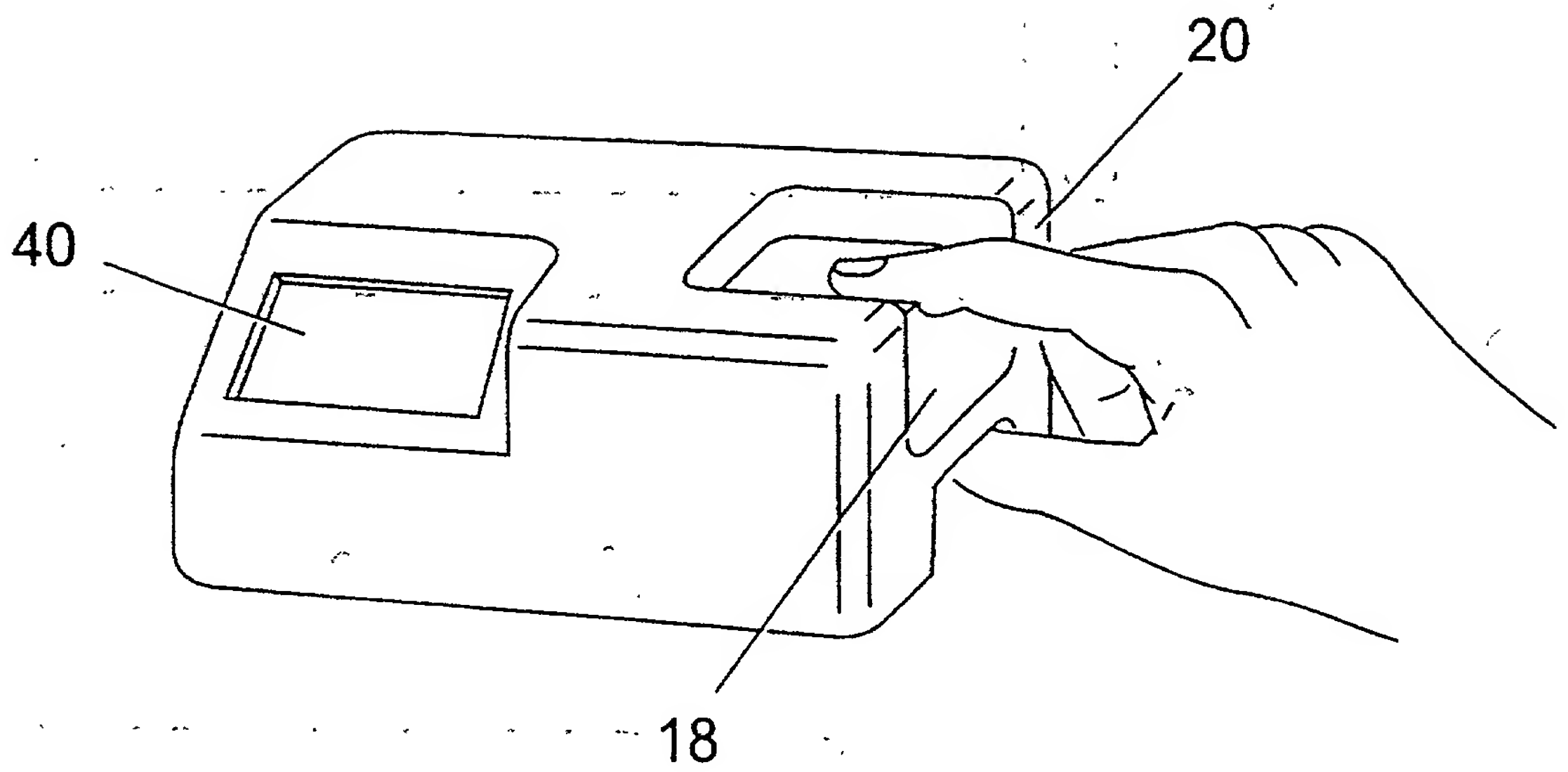


Fig. 5

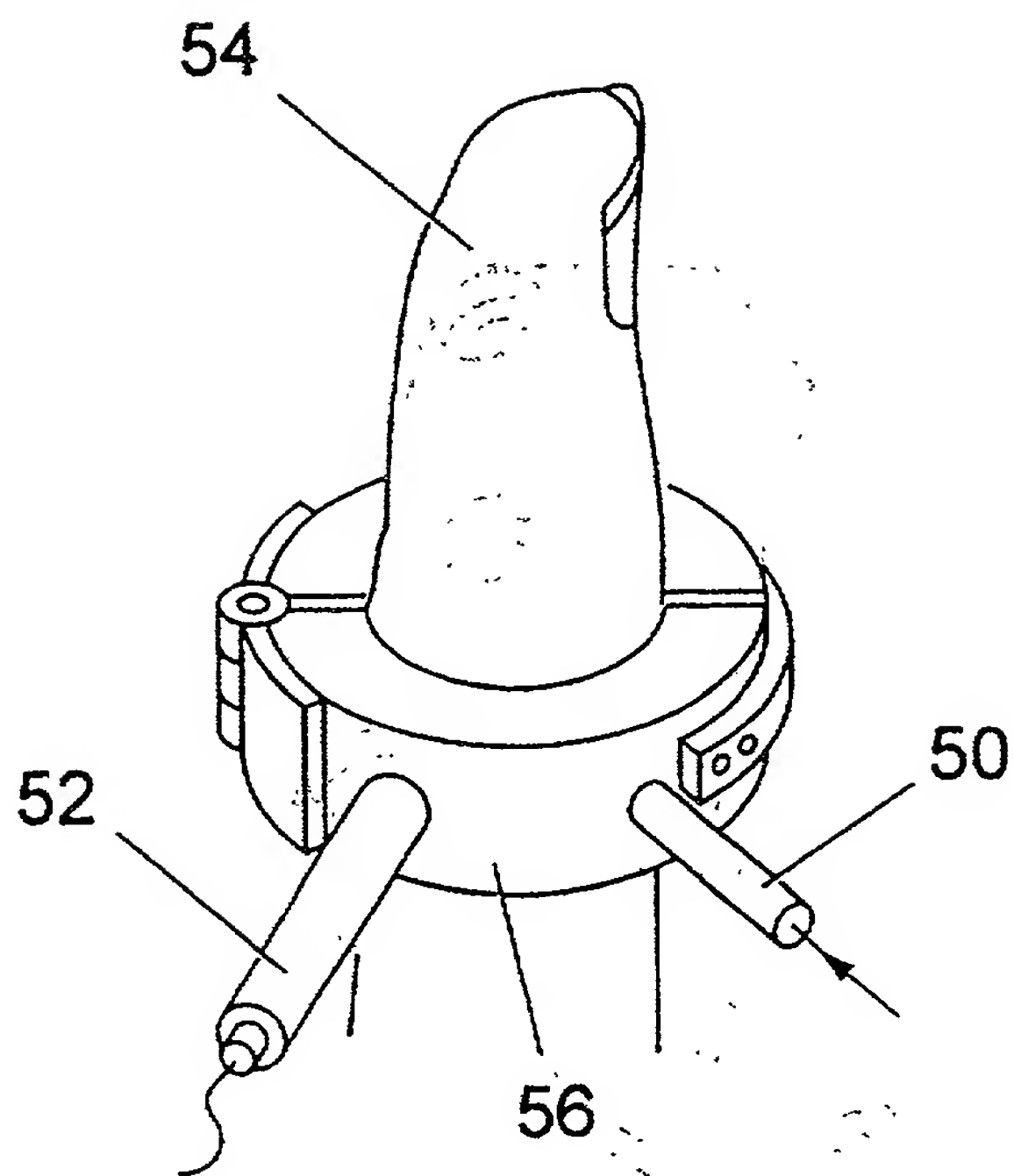


Fig. 6

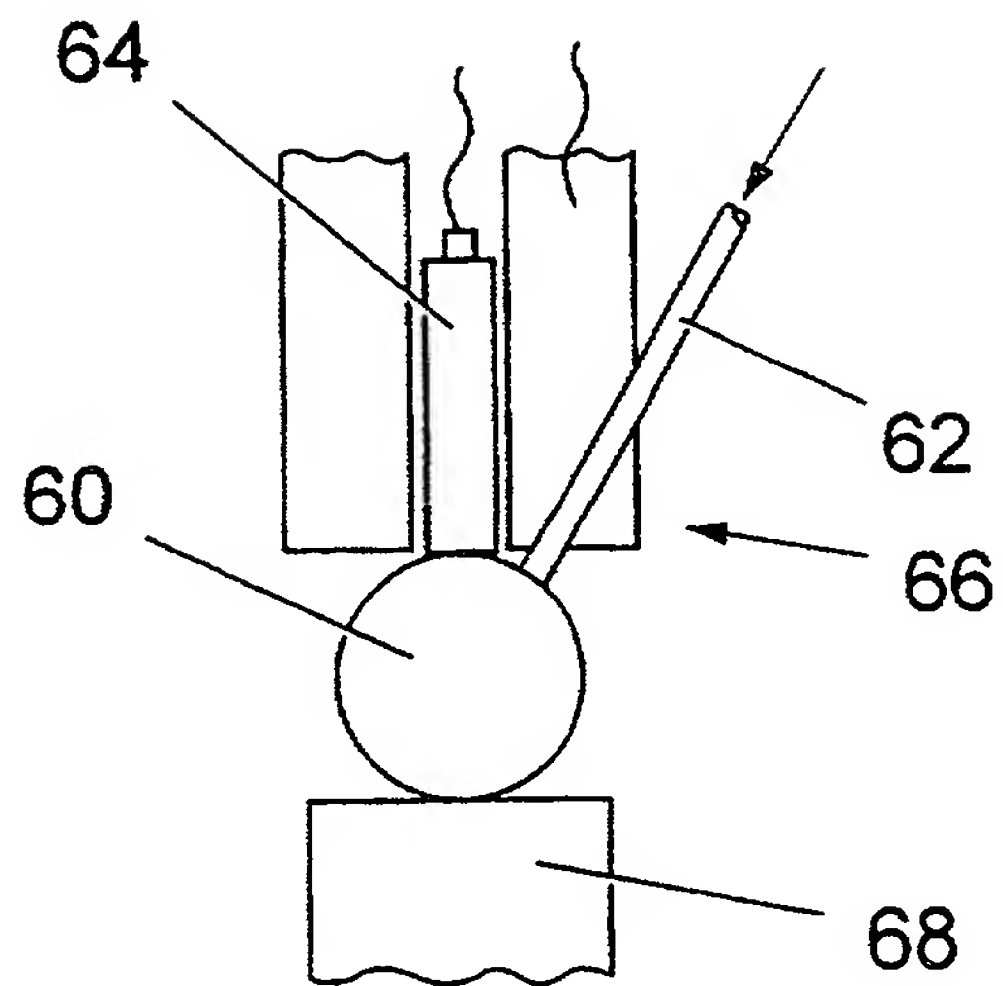


Fig. 7

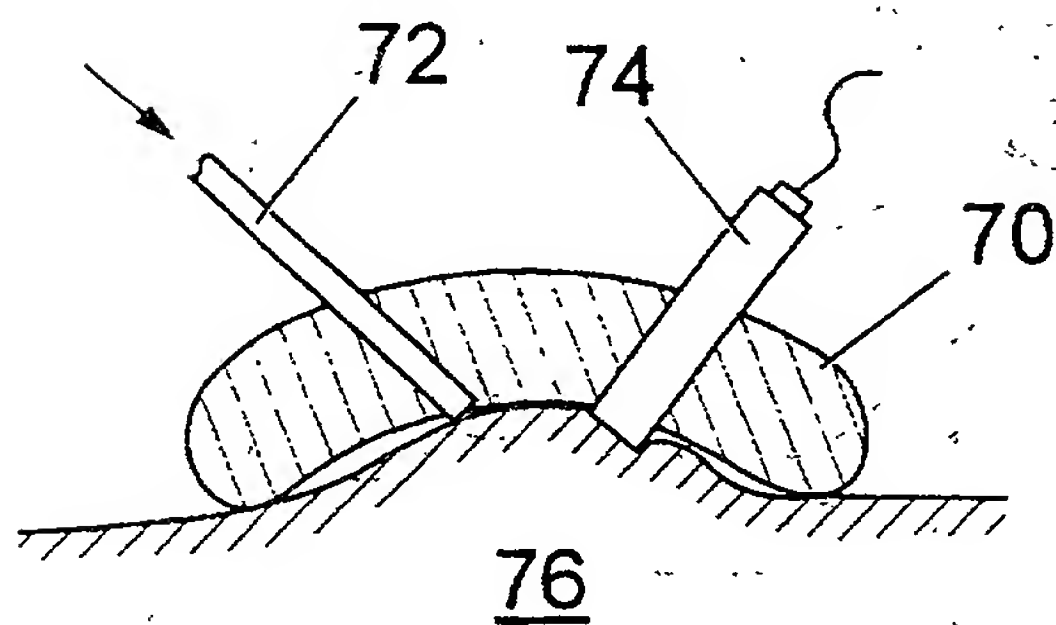


Fig. 8a

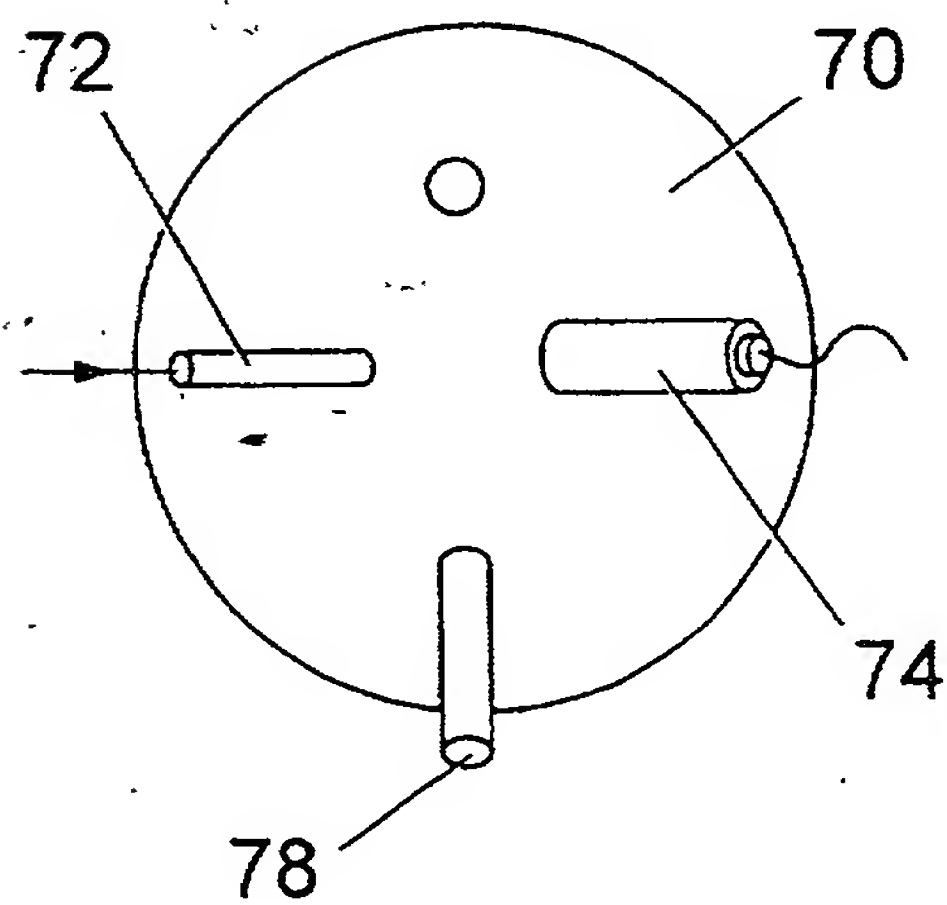


Fig. 8b

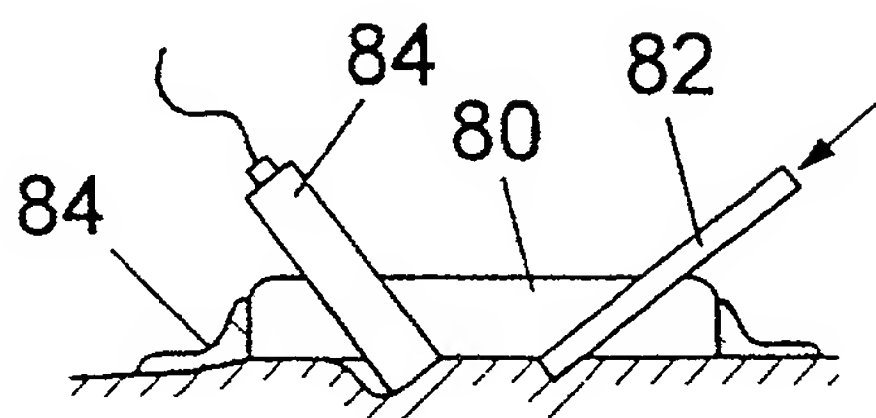


Fig. 9

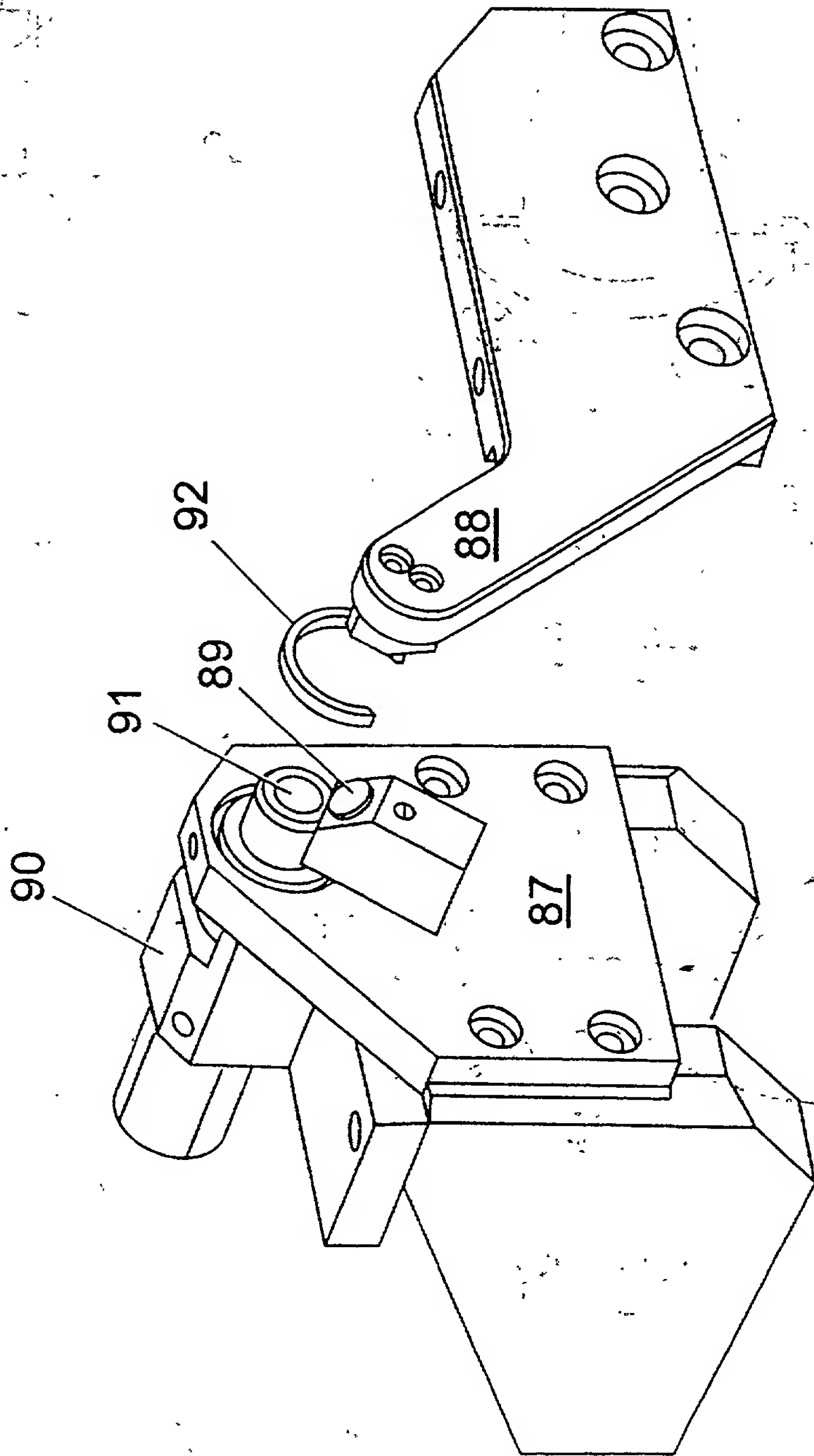


Fig. 10

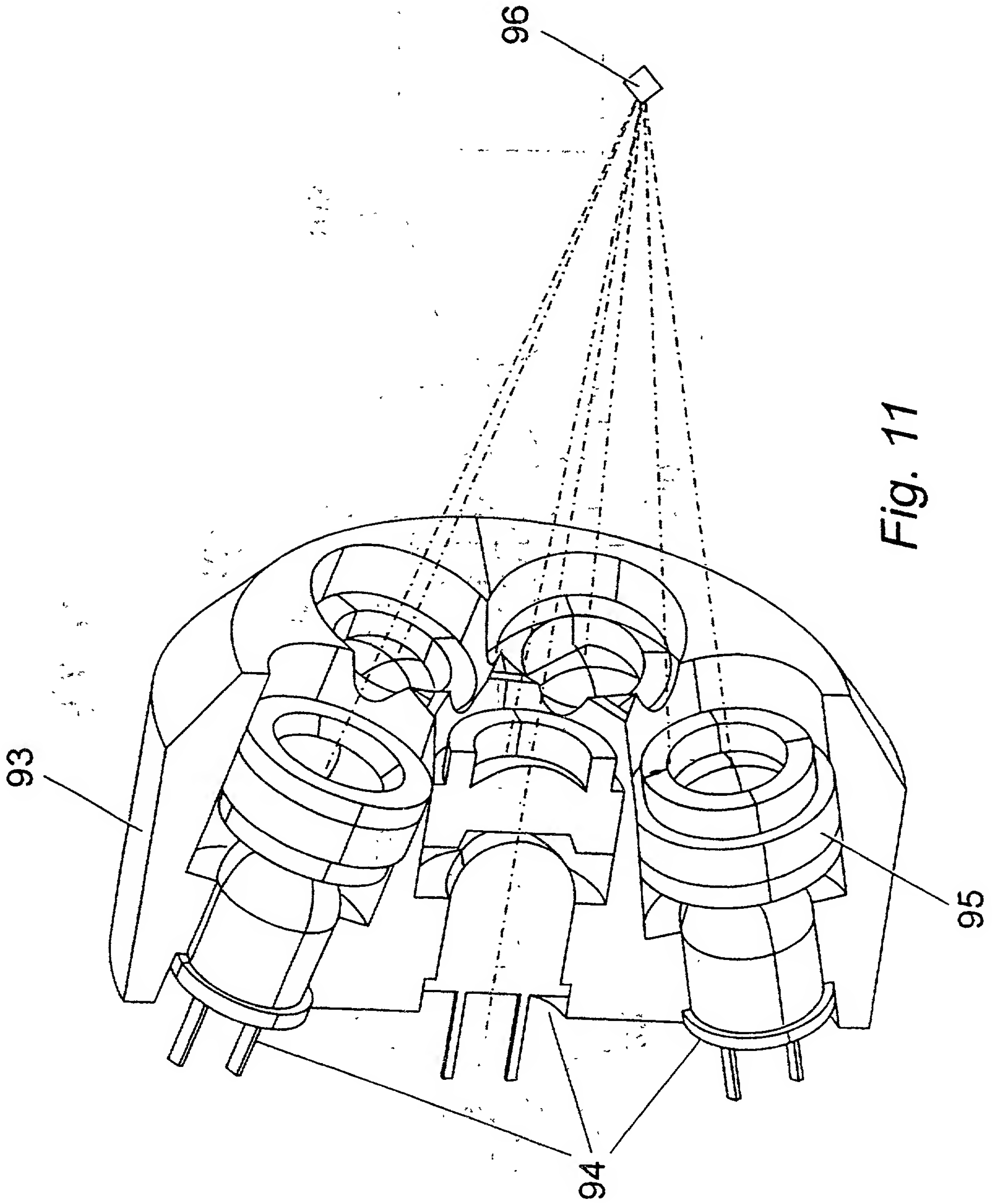


Fig. 11

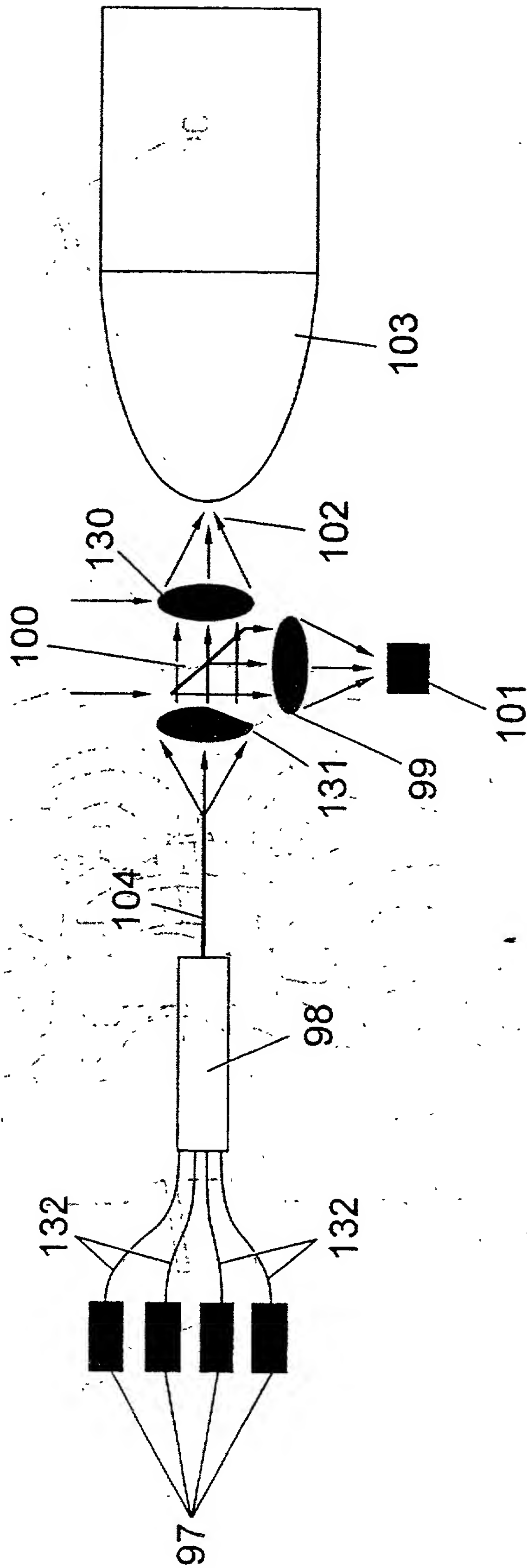


Fig. 12

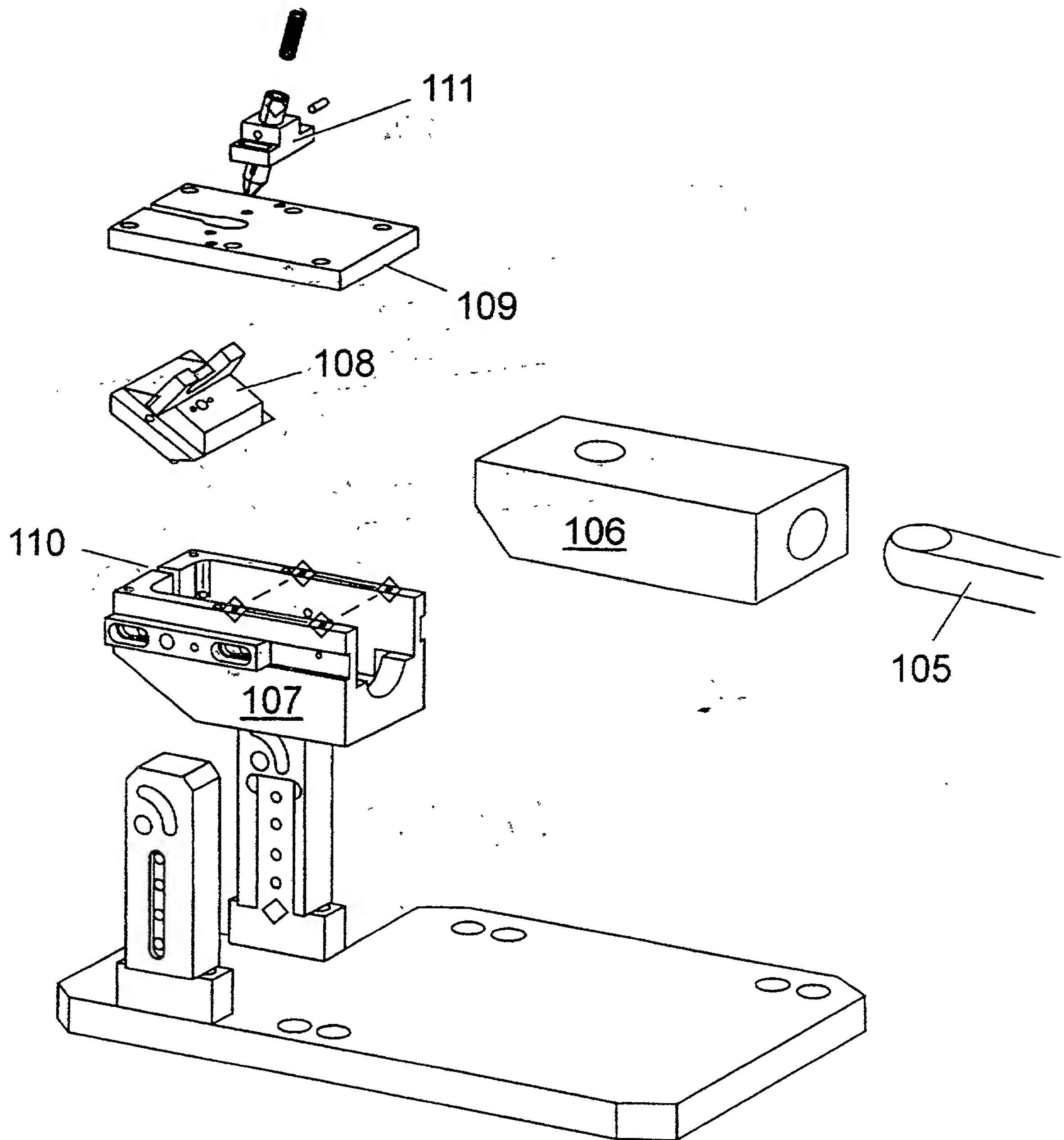


Fig. 13

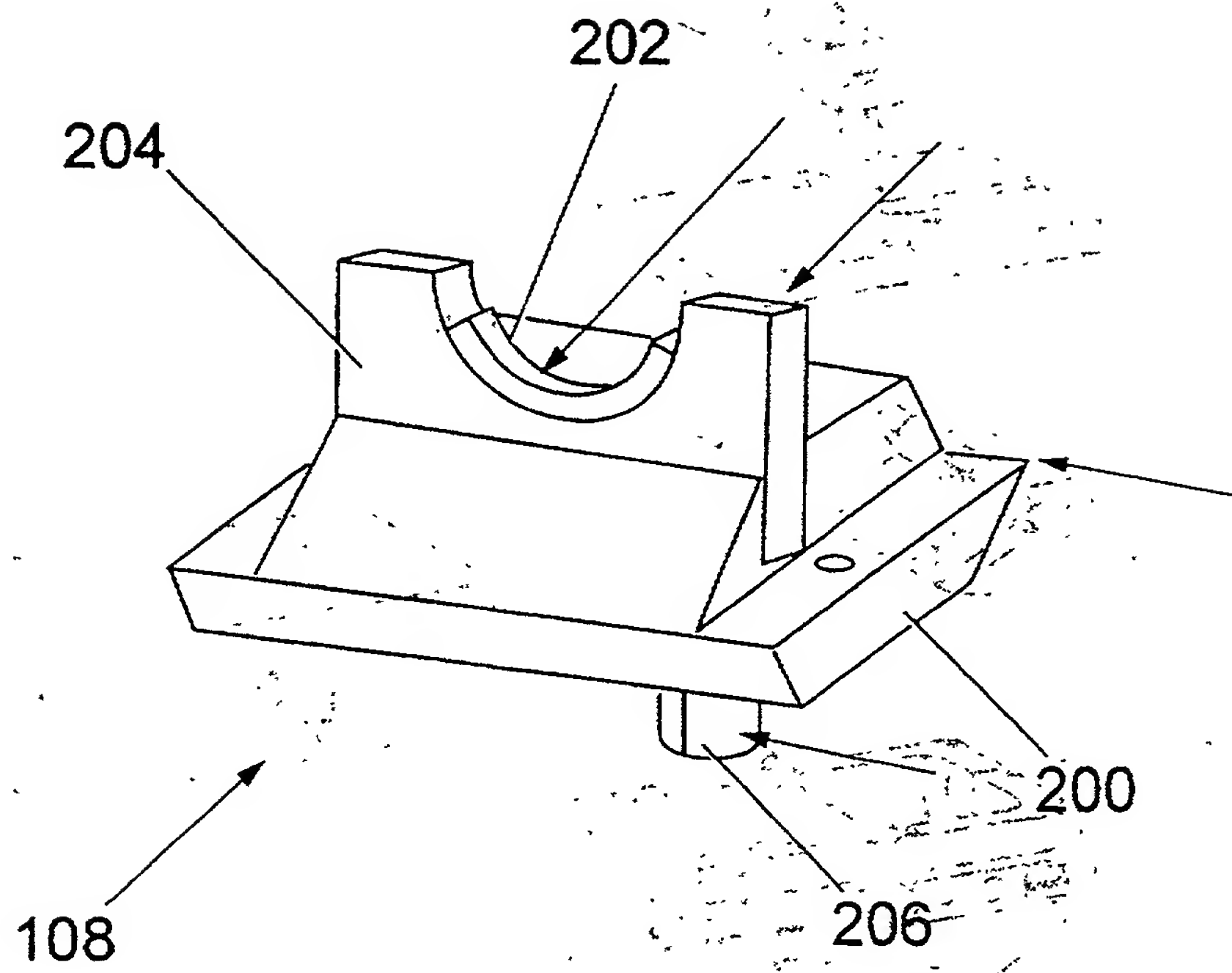


Fig. 13a

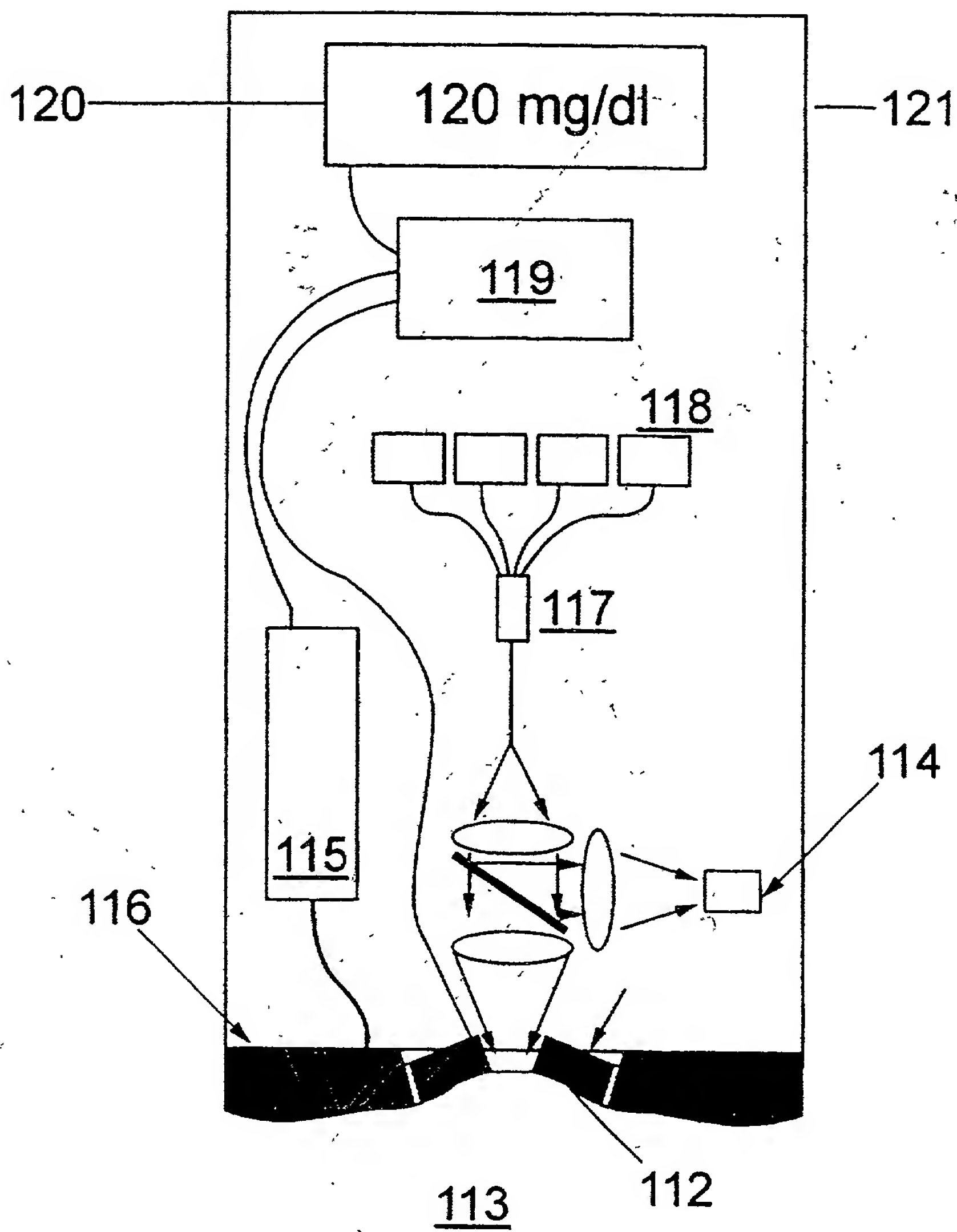


Fig. 14

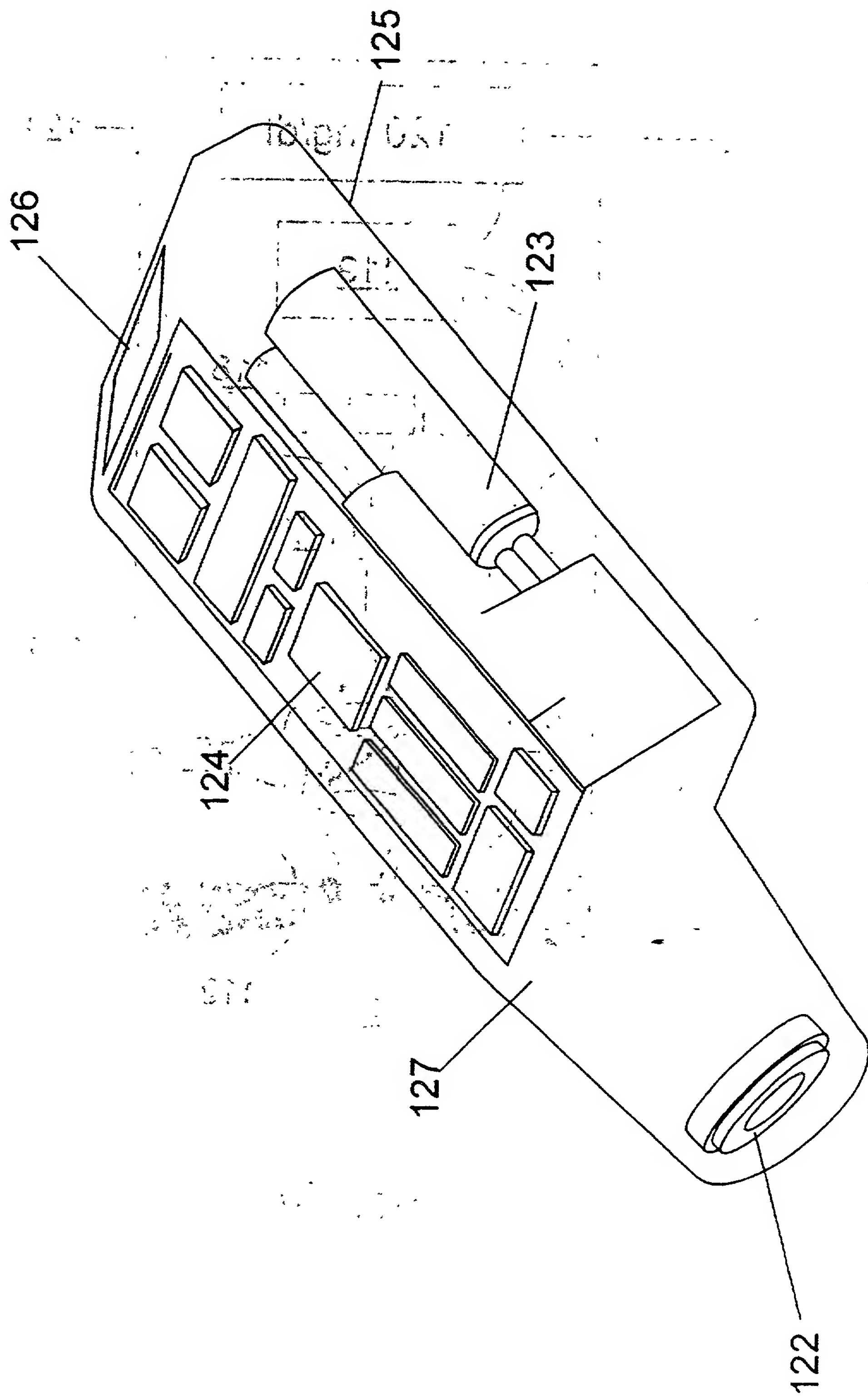


Fig. 15

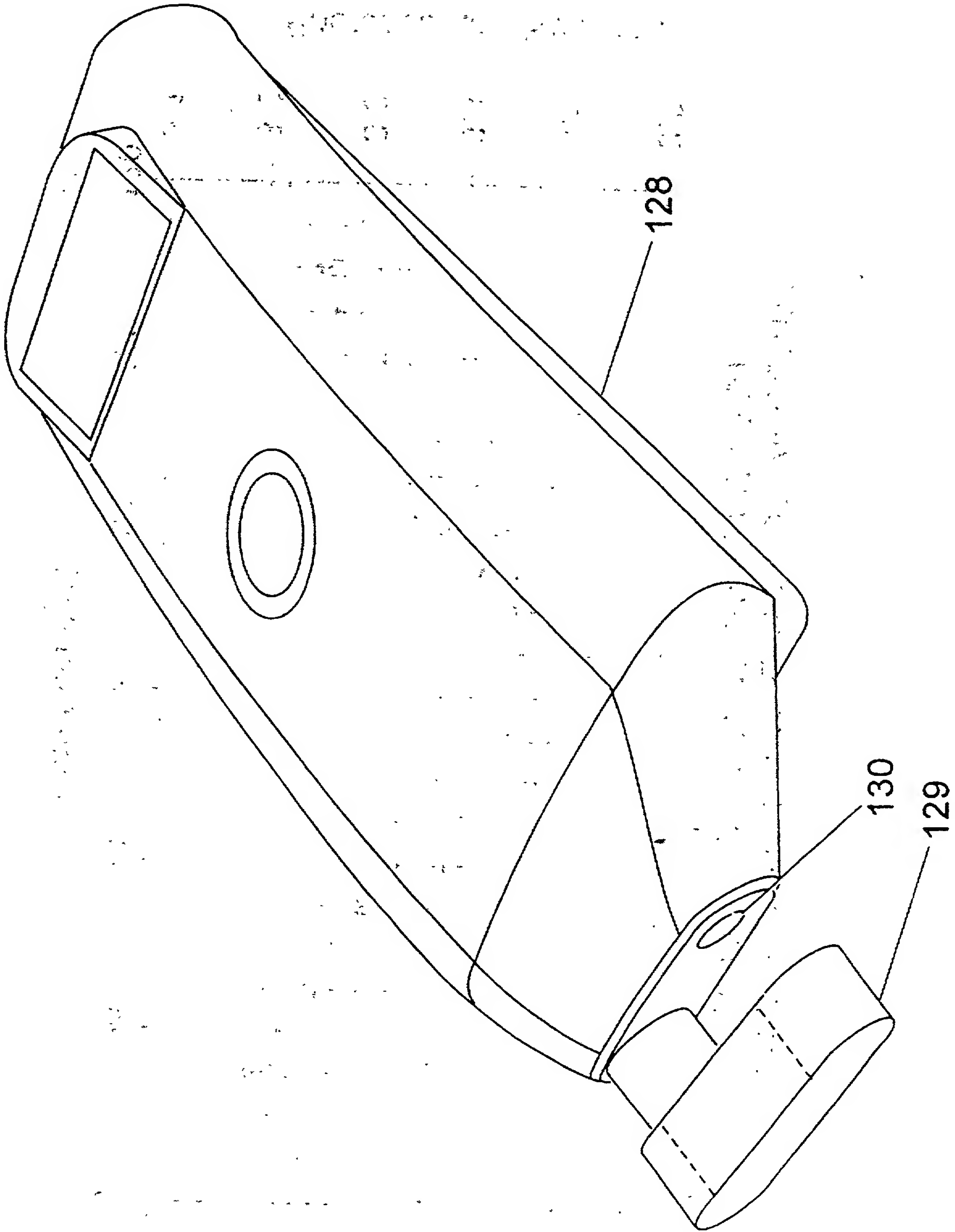


Fig. 16

CLINICAL BLOOD GLUCOSE vs. PHOTOACOUSTIC MEASUREMENT FOR NORMAL SUBJECT

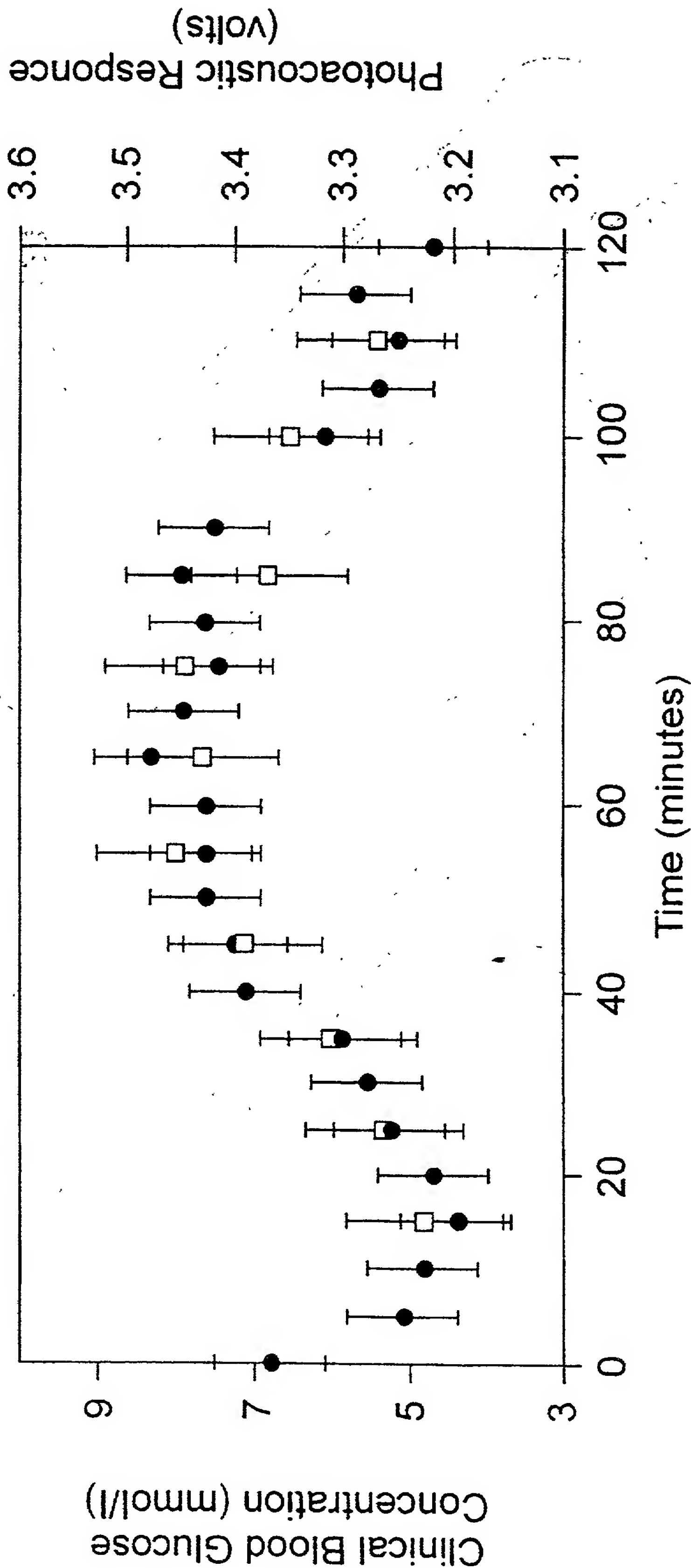


Fig. 17

CLINICAL BLOOD GLUCOSE vs. PHOTOACOUSTIC MEASUREMENT FOR TYPE 1 DIABETIC

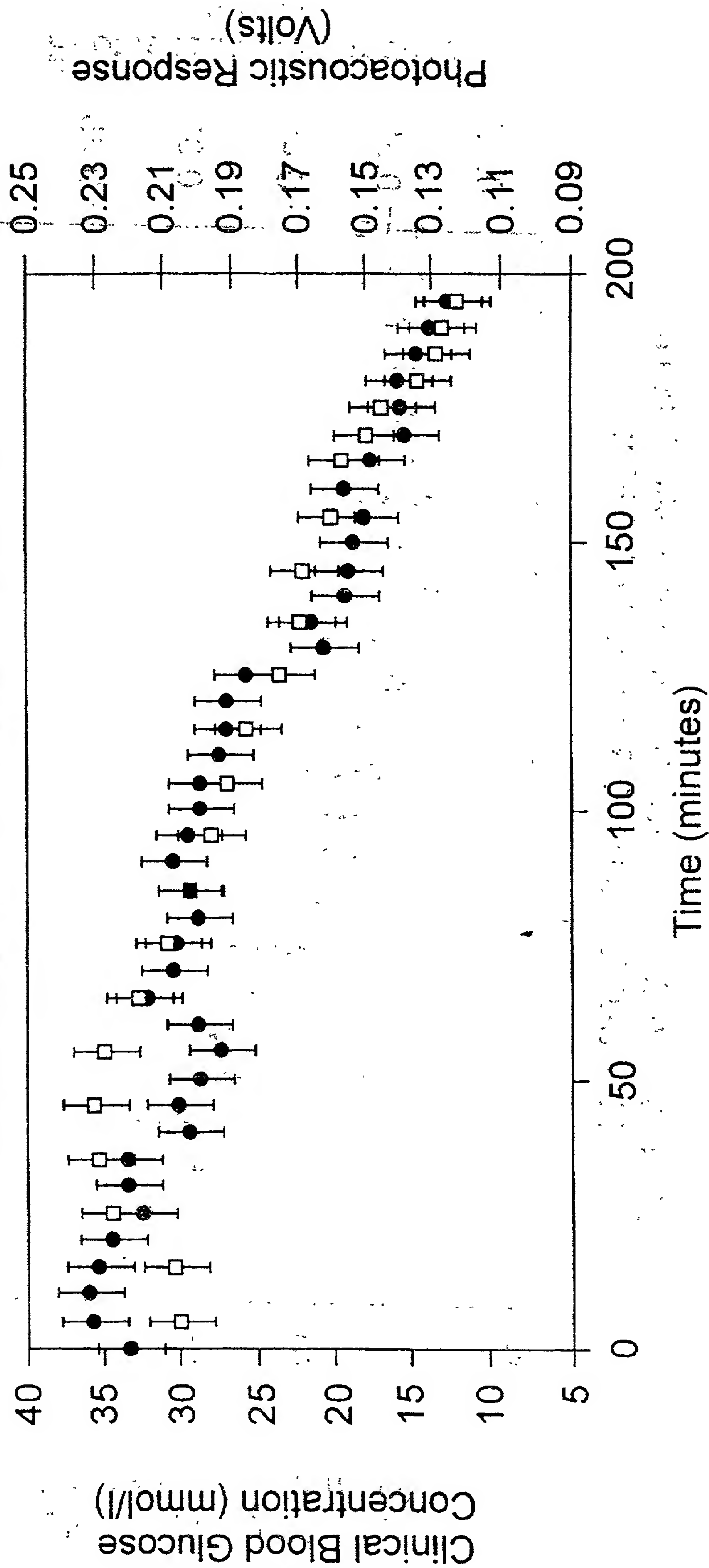


Fig. 18

CLINICAL BLOOD GLUCOSE vs. PHOTOACOUSTIC MEASUREMENT FOR TYPE 2 DIABETIC

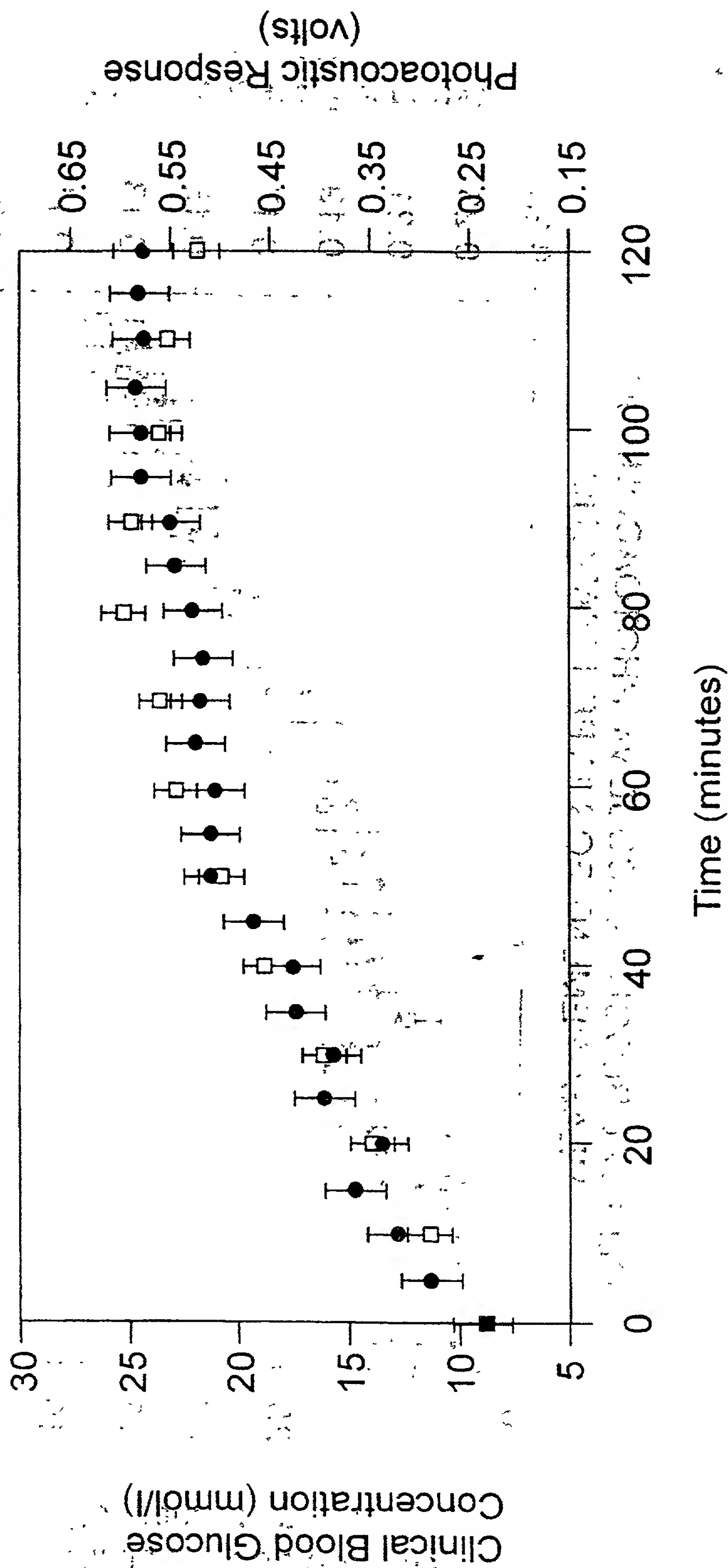


Fig. 19

1 Biological Measurement System

2
3 This invention relates to apparatus for use in non-
4 invasive in vivo monitoring of physiological substances
5 such as blood and the like.
6

7 One particular, but not exclusive, application of the
8 present invention is in the monitoring of blood
9 glucose, for example in the management of diabetes
10 mellitus. It is accepted that the management of
11 diabetes can be much improved by routine monitoring of
12 blood glucose concentration and clinicians suggest that
13 monitoring as often as four times per day is desirable.
14

15 The monitoring technique currently available for use by
16 patients involves using a spring loaded lancet to stab
17 the finger to obtain a blood sample which is
18 transferred to a glucose test strip. The concentration
19 is derived either by reading the test strip with a
20 reflectance meter or by visual comparison of colour
21 change against a colour scale. Many diabetics find the
22 testing onerous as the technique is painful,
23 inconvenient, messy, potentially embarrassing and
24 offers a site for the transmittance and acceptance of
25 infection.

1 Techniques have also been developed for non invasive
2 measurement using transmittance or reflectance
3 spectroscopy. However the required instruments are
4 expensive and it is difficult to obtain accurate and
5 repeatable measurements.

6
7 There are also known various types of in vivo chemical
8 sensors. These rely on implanting minimally invasive
9 sensors under the skin surface, but such sensors have
10 poor long term reproducibility and bio-compatibility
11 problems.

12
13 There is therefore a need for improved means for
14 routine monitoring of blood glucose in a manner which
15 is simple and straightforward to use.

16
17 The present invention makes use of photoacoustic
18 techniques. The fundamentals of photoacoustic
19 techniques are well known per se. A pulse of light,
20 typically laser light, is applied to a substance
21 containing an analyte of interest in solution or
22 dispersion, the wavelength of the applied light being
23 chosen to interact with the analyte. Absorption of the
24 light energy by the analyte gives rise to microscopic
25 localised heating which generates an acoustic wave
26 which can be detected by an acoustic sensor. These
27 techniques have been used to measure physiological
28 parameters in vitro.

29
30 US Patents 5348002 and 5348003 (Caro) propose the use
31 of photoacoustics in combination with photoabsorption
32 for the measurement of blood components in vivo.

33 However, the arrangement proposed by Caro has not been
34 demonstrated as a workable system and may suffer from
35 interference to a degree which would preclude useful
36 acoustic signals, and since they would also suffer from

1 interference and resonance effects from hard structures
2 such as bone.

3
4 It has also been proposed by Poulet and Chambron in
5 Medical and Biological Engineering and Computing,
6 November 1985, Page 585 to use a photoacoustic
7 spectrometer in a cell arrangement to measure
8 characteristics of cutaneous tissue, but the apparatus
9 described would not be suitable for measuring blood
10 analytes.

11
12 Published European Patent Application 0282234A1
13 (Dowling) proposes the use of photoacoustic
14 spectroscopy for the measurement of blood analytes such
15 as blood glucose. This disclosure however does not
16 show or suggest any means which would permit the
17 required degree of coupling to body tissues for use in
18 vivo.

19
20 Accordingly, the present invention provides a sensor
21 head for use in photoacoustic in vivo measurement,
22 comprising a housing shaped to engage a selected body
23 part, light transmission means terminating in said
24 housing so as to transmit light energy from a light
25 source to enter the body part along a beam axis, and
26 acoustic transducer means mounted in the housing to
27 receive acoustic waves generated by photoacoustic
28 interaction within the body part, the acoustic
29 transducer means being disposed in the housing to
30 receive said acoustic wave in a direction of high
31 acoustic energy.

32
33 The expression "direction of high acoustic energy" is
34 used herein to denote a direction other than the
35 forward direction of the light beam. Preferably, the
36 transducer means is disposed so as to intercept

1 acoustic energy propagating at right angles to the
2 optical beam axis, or at an angle to the optical beam
3 axis which may be down to about 20° , typically about
4 45° .

5
6 An exact measure of the angle of high acoustic energy
7 can be worked out but is dependent upon the specific
8 geometry of the light source, the properties of the
9 tissue and the absorption coefficient of the tissue.
10 One model for understanding the propagation of the
11 acoustic energy in any homogenous media was developed
12 by Huyghens and is called the principle of
13 superposition. In this model each volume element that
14 is illuminated by the light generates an acoustic
15 pressure wave that radiates outward in a spherical
16 manor. The magnitude of the pressure wave at each
17 volume element depends on the intensity of the optical
18 beam at that location, the absorption coefficient of
19 the material at that location, the wavelength of light
20 and on several other physical properties of the
21 material such as the speed of sound and the specific
22 heat. The signal measured at the detector is just the
23 superposition of all pressure waves from all points
24 that are illuminated by the source light. An
25 analytical solution for the pressure wave has been
26 worked out for a few cases in aqueous material. The
27 analytical case that best matches the in-vivo
28 measurements is that of a cylindrical optical beam
29 propagating in a weakly absorbing material. In this
30 case the direction of highest acoustic energy is
31 perpendicular to the optical axis. The base detector
32 location is with the plane of the detector
33 perpendicular to the acoustic energy, or parallel to
34 the optical axis. This is because the acoustic
35 detector has the highest sensitivity when the acoustic
36 energy strikes the detector perpendicular to the plane

1 of the detector. This analytical model is not
 2 completely accurate for the in-vivo measurement case
 3 because of scattering of the tissue and because the
 4 tissue absorbs more than the model predicts. These
 5 differences indicate that a different position for the
 6 detector will be optimal. A detailed numeric model is
 7 required to determine the best detector location and is
 8 dependent upon the beam properties (focused to a point,
 9 colligated, etc.); body site (finger, earlobe, arm
 10 etc.) and wavelength. One skilled in the art can
 11 readily develop an appropriate mode. However, suitable
 12 locations for a detector will generally be at an angle
 13 to the optical axis. Angles between 40 and 90 degrees
 14 should be suitable.

15
 16 In one preferred arrangement, the acoustic transducer
 17 means is arranged parallel to the optical beam axis.
 18 This arrangement is particularly suitable for use where
 19 the selected body part is the distal portion of a
 20 finger, in which case the housing may include a
 21 generally half-cylindrical depression in which the
 22 finger may be placed with the light transmission means
 23 aimed at the end of the finger.

24
 25 Preferably, the acoustic transducer means comprises a
 26 piezoelectric transducer which most preferably is of a
 27 semi-cylindrical shape. This transducer may be
 28 provided with a backing of lead or other dense
 29 material, and the backing may have a rear surface
 30 shaped to minimise internal acoustic reflection.

31
 32 Alternative transducer means include a capacitor-type
 33 detector, which is preferably small and disk-shaped; an
 34 integrated semiconductor pressure sensor; and an
 35 optical pressure sensor, for example based on an
 36 optical fibre.

1 In an alternative arrangement, the plane of the
2 transducer may be arranged to be perpendicular to the
3 optical axis to detect the acoustic wave which is
4 propagating in a direction opposite to the direction of
5 the light beam. For example, the acoustic transducer
6 means may be part-spherical with an aperture to allow
7 access for the light beam. This may be particularly
8 suitable for engagement with a body part other than the
9 finger, for example the back of the arm.

10
11 The generation of a surface acoustic wave is an
12 inherent aspect of the in vivo pulsed photoacoustic
13 generation in tissue and may be used to characterize
14 tissue properties such as density. A surface wave
15 detector may be provided in the sensing head assembly.

16
17 Preferably means are provided for ensuring a consistent
18 contact pressure between the selected body part and the
19 acoustic transducer means. In the case where the
20 selected part is the distal portion of the finger, said
21 means may be provided by mounting the portion of the
22 housing engaged by the finger in a resiliently biased
23 fashion against the remainder of the housing, and
24 providing means to ensure that measurement is effected
25 when the predetermined force or pressure is applied by
26 the subject against the resilient bias. In the case
27 where the selected part is the earlobe, said means may
28 be provided by placing the ear between two plates and
29 applying pressure to the ear with springs or weights or
30 other force method. The two plates holding the ear may
31 contain a removable insert. The two plates may be flat
32 or may be of another shape to optimally position the
33 detector with respect to the beam axis.

34
35 In addition, the present invention provides a sensor
36 head for use in photoacoustic in-vivo measurements,

1 comprising a housing shaped to receive a removable
2 insert, a removable insert that engages a selected body
3 part, the insert being fitted to an individual,
4 allowing for a range of sizes of body parts to be used,
5 and further comprising light transmission means
6 terminating in or near said removable insert so as to
7 transmit light energy from a light source or sources to
8 enter the body part along a beam axis, and an acoustic
9 transducer means mounted in the housing or in the
10 removable insert to receive acoustic waves generated by
11 photoacoustic interaction within the body part to
12 receive said acoustic waves in a direction of high
13 acoustic energy.

14
15 From another aspect the present invention provides an
16 in vivo measuring system comprising a sensor head as
17 hereinbefore defined in combination with a light source
18 coupled with the light transmission means, and signal
19 processing means connected to receive the output of the
20 acoustic transducer means and to derive therefrom a
21 measurement of a selected physiological parameter.

22
23 Preferably, the light transmission means is a fiber
24 distribution system where each light source is
25 connected to an individual fiber and when multiple
26 light sources are used the multiple fibres are joined
27 by some standard fiber combining method, such as a
28 wavelength division multiplexer or a fiber coupler.
29 The fiber that comes from the light source, or contains
30 the combined light for a multiple source system, is
31 then terminated in proximity to the body part being
32 measured. The fiber could be in contact with the body
33 part or alternatively standard optics, such as lenses,
34 beamsplitters and such, could be employed to convey the
35 light from the end of the fiber to the body part. A
36 reference detector or several reference detectors and

1 beamsplitters can be added to the optical distribution
2 system to determine the energy of the light entering
3 the body part.

4
5 Alternatively, the optical distribution system may
6 contain mechanical holders, lenses and such to convey
7 the light from the source, or sources, to a location in
8 proximity to the body part being measured. A reference
9 detector or several reference detectors and
10 beamsplitters can be added to the optical distribution
11 system to determine the energy of the light entering
12 the body part.

13
14 The acoustic signal from the detector contains
15 information in both time and frequency, and there may
16 be information from several sources. The processing
17 means is preferably a multi-dimensional processing
18 method, such as Classical Least Squares (CLS) or
19 Partial Least Squares (PLS). Alternatively the
20 processing method may be more flexible, such as a
21 Neural Network. In addition to these methods the
22 signals may be analysed for their frequency content
23 using such techniques as Fourier Analysis or Frequency
24 Filtering. In addition techniques may be employed that
25 use time information such as the time delay from source
26 trigger. Techniques that combine both frequency and
27 time information may be employed, such as Wavelet
28 analysis.

29
30 The light source is preferably a laser light source and
31 is most suitably a pulsed diode laser, but may utilise
32 a set of such lasers or utilise a tunable laser source.
33 In a particularly preferred form, suitable for use in
34 measuring blood glucose concentration, a laser diode is
35 used with a wave length in the range of approximately
36 600 nm to 10,000 nm and a pulse duration of the order

1 of 5 to 500 ns.

2

3 The delivery to the measurement site may be either
4 directly or by optical fibre with a suitable optical
5 element to focus the beam into the tissue.

6

7 Preferably means are provided for time multiplexing
8 multiple sources when multiple sources are used. Each
9 source is switched on, and it generates an optical
10 pulse, or a set of optical pulses. This pulse, or set
11 of pulses, generates an acoustic signal that is
12 detected by the detector. Each source is pulsed in
13 sequence until all sources have been used to generate
14 their own signal.

15

16 The measuring system may conveniently be in the form of
17 a self contained system including a power supply and a
18 readout, which may be carried on the person and used at
19 any convenient time.

20

21 It is also possible for such a self contained system to
22 incorporate, or to be provided with facilities for
23 connection to, a cellular telephone, two-way pager or
24 other communication device for routine transmission of
25 measurements taken to a central data collection point.

26

27 In addition the measuring system may have provision for
28 manipulating the body part under measurement and for
29 performing additional measurement of the tissue to get
30 other information about the state of the physiology of
31 the issue. It is well-known in the art that squeezing
32 a section of tissue to increase the pressure and then
33 releasing the pressure will cause changes in the total
34 blood volume in the measurement site. The present
35 invention may allow for this type of manipulation
36 including the squeezing of a body part, such as an

1 earlobe, and making photo acoustic measurements at
2 several different pressures. The present invention may
3 also allow for the measurement of the temperature of
4 the body site and to apply a correction to the
5 measurements based upon the temperature of the body
6 site.

7
8 Another type of physiological manipulation is body
9 temperature. It is known in the art that several
10 parameters involved in the detection of the photo
11 acoustic signal, such as the speed of sound, are
12 dependent upon the temperature of the medium the signal
13 is propagating through (the tissue). Also the
14 perfusion of the blood in the small capillaries is
15 dependent upon the temperature of the tissue.
16 Additional information about the tissue can be obtained
17 if the photo acoustic measurement is made at several
18 temperatures, both higher and lower than ambient
19 temperature. This additional information is used to
20 better eliminate interferences to the determination of
21 the analyte under investigation. These are only two
22 examples of manipulating the body site and are not
23 intended to be an exhaustive list, and they can be used
24 in combination with other manipulation techniques.

25
26 The in-vivo measuring system may comprise a means for
27 storing calibration coefficients or operation
28 parameters or both calibration coefficients and
29 operational parameters, in order to calibrate the
30 instrument and to set critical operational parameters.

31
32 Another aspect of the present invention provides a
33 means for adjusting the calibration coefficients and
34 operational parameters to be specific to a particular
35 person and may be used to adjust for such things as
36 body part size, skin color, skin condition, amount of

1 body fat, efficiency of the detector and efficiency of
2 the source(s).

3
4 In addition the present invention may provide for
5 having the specific calibration coefficients and
6 operational parameters be contained in a storage site
7 located in the removable insert. This allows for the
8 system to be both mechanically and operationally
9 configured to a particular individual. Additionally
10 the invention may allow for the calibration
11 coefficients and operational parameters to be stored in
12 two locations, one in the non-removable housing and one
13 in the removable insert with some of the coefficients
14 and parameters stored in each location. This allows
15 for reader system coefficients to be stored in the
16 reader and coefficients specific to an individual to be
17 stored in the removable insert for that person,
18 enabling many people to use the same reader.

19
20 Another aspect of the present invention provides means
21 for connecting the non-invasive measuring system to an
22 invasive measuring system for the purpose of
23 calibrating or adjusting the operational parameters of
24 the non-invasive measuring system. Such connection may
25 be accomplished, but is not limited to, communication
26 by a wire, IR link or radio waves.

27
28 Another aspect of the present invention provides a
29 method for removing instrument drift from the
30 measurement comprising the steps of:

- 31
- 32 1. Placing a standard in the reader in place of the
33 body part.
 - 34
 - 35 2. Measuring the signal from the standard for each
36 wavelength and storing the values in the

1 calibration storage location.

2

3 3. Before making a measurement of a body part,
4 placing the calibration standard in the reader.

5

6 4. Measuring the signal from the standard for each
7 source.

8

9 5. Comparing the just measured standard values to the
10 stored calibration values.

11

12 6. Calculating correction factors for each source
13 wavelength.

14

15 7. Removing the standard and placing the body part in
16 the reader.

17

18 8. Measuring the signal from the body part for each
19 source.

20

21 9. Adjusting the measured values using the calculated
22 correction factors.

23

24 In addition to the signal correction factors a
25 correction factor can be calculated for the instrument
26 temperature. This can be applied to each signal with a
27 different correction coefficient.

28

29 The invention further provides a method of measuring a
30 biological parameter in a subject, the method
31 comprising the steps of:

32

33 directing one or more pulses of optical energy
34 from the exterior into the tissue of a subject
35 along a beam axis, the optical energy having a
36 wavelength selected to be absorbed by tissue

1 components of interest, thereby to produce a
2 photoacoustic interaction;

3
4 detecting acoustic energy resulting from said
5 photoacoustic reaction by means of a transducer
6 positioned to intercept acoustic energy
7 propagating in a direction other than the forward
8 direction of said beam axis; and

9
10 deriving from said detected acoustic energy a
11 measure of the parameter of interest; and a
12 corresponding apparatus.

13
14
15 Embodiments of the invention will now be described, by
16 way of example only, with reference to the accompanying
17 drawings in which:-

18
19 Figs. 1A, 1B and 1C are side views illustrating the
20 principle of operation of one embodiment of the
21 present invention;

22
23 Fig. 2 is a schematic perspective view showing a
24 sensor head for use in carrying out the
25 measurement illustrated in Fig. 1;

26
27 Fig 3. is a cross section view of the sensor head
28 of Fig. 2;

29
30 Fig. 4 is a side view of the sensor head of Fig.
31 2;

32
33 Fig. 5 is a schematic perspective view of an
34 apparatus incorporating the sensor head of Figs. 2
35 to 4;

36

1 Fig. 6 is a perspective view illustrating an
2 alternative form of sensor head;

3
4 Fig. 7 is a schematic end view showing another
5 form of sensor head;

6
7 Figs. 8a and 8b are a cross-sectional side view
8 and a plan view, respectively, of a further sensor
9 head;

10
11 Fig. 9 is a cross-sectional side view of one more
12 embodiment of sensor head;

13
14 Fig. 10 is a perspective view of one type of ear
15 interface apparatus;

16
17 Fig. 11 is a schematic of a multiple laser optical
18 distribution system using lenses, mechanical
19 mounts and a reference detector;

20
21 Fig. 12 is a schematic of a multiple laser optical
22 distribution system using fiber optic cables and a
23 fiber Wavelength Division Multiplexer (WDM), a
24 beam splitter and a reference detector;

25
26 Fig. 13 is a perspective view of a finger
27 interface apparatus with removable inserts that
28 are moulded to fit one individual;

29
30 Fig. 13A shows part of the apparatus of Fig. 13 in
31 greater detail;

32
33 Fig. 14 is a schematic of a semi-spherical
34 detector that contains a hole for the light beam,
35 with a vacuum system and a fiber distribution
36 system;

Fig. 15 is a perspective view showing one form of the instrument utilizing the vacuum body interface, a semi-spherical detector and the multiple laser source with lenses and mechanical housing;

Fig. 16 is a perspective view showing one form of the instrument using an ear lobe body interface, with the added feature of being able to manipulate the pressure on the ear lobe; and

Figs. 17, 18 and 19 are graphs illustrating an example.

Referring to Fig 1, an important feature of the present invention lies in introducing light energy along an axis into an area of soft tissue and detecting the resulting acoustic response transverse to that axis. Accordingly, in the arrangement of Fig 1A light energy from a diode laser (not shown) is transmitted via a fibre-optic guide 10 to the tip of a finger 12. The photoacoustic interaction occurs in an approximately cylindrical region indicated at 14 from which acoustic energy is radiated in a generally cylindrical manner and is detected by a transversely arranged acoustic transducer 16.

In Figs 1B and 1C, the principle is similar. The finger 12 is pressed against a support with force F. In Fig 1B, the incident light beam indicated at L is directed as in Fig 1A, and the transducer 16 is at an angle of 45 degrees thereto. In Fig 1B, the angle is 90 degrees as in Fig 1A, but the incident beam is directed differently into the fingertip.

1 In the present embodiment, the laser wavelength is
2 chosen to achieve high degree of absorption by glucose
3 present in the blood. A suitable wavelength is in the
4 range approximately 1000 to 3000 nm. The laser pulse
5 duration is chosen to be short, typically of the order
6 of 5 to 500 ns, in order to minimise thermal diffusion
7 and thus to optimise the acoustic waveform. For the
8 same reasons, it is desirable to use a spot size which
9 is sufficiently small to minimise thermal diffusion,
10 typically a spot size of the order of 0.05 mm to
11 0.50 mm.

12
13 The efficiency of the photoacoustic detection is also
14 influenced by the positioning and dimensions of the
15 acoustic transducer in relation to the characteristic
16 extinction length of the tissue at the principal
17 wavelengths chosen for measurement. In the fingertip
18 arrangement of Fig. 1, the system efficiency will be
19 improved by optimising the length of the transducer
20 crystal parallel to the axis of the finger, but the
21 length should not be so great as to give rise to
22 undesired signals which would occur at the point of
23 entry of the optical energy into the finger and by
24 reason of interaction of the acoustic energy with bone
25 or other hard tissue.

26
27 A second limit on the size of the acoustic detector
28 derives from the wavelength of the acoustic wave in the
29 tissue. Again making use of Huyghens principal of
30 superposition we view each point of tissue, that is
31 illuminated by the incoming light, as a point source
32 that generates a spherical pressure wave. The signal
33 measured at the detector is just the superposition of
34 all pressure waves from all points that are illuminated
35 by the source light. Normally if the size of the
36 detector is increased then the signal should also

1 increase because more energy is received by the
 2 detector. However if the acoustic detector is too
 3 large then a pressure wave generated from a tissue
 4 element will create a pressure wave that will strike
 5 the both ends of the detector. If the paths length
 6 from the tissue element to the first end of the
 7 detector is different than the path length to the
 8 second end of the detector and if this difference in
 9 path length is about one half of the acoustic signal
 10 wavelength then the signal will destructively interfere
 11 with itself and will reduce the magnitude of the
 12 measured signal.

13
 14 Referring to Fig 2, one manner of carrying out the
 15 arrangement shown in Fig 1 makes use of a sensor head
 16 having a finger rest 18 which is slidably moveable
 17 within housing 20 closed by a front plate 22. The user
 18 inserts his finger in a semi-cylindrical depression 24
 19 in the finger rest 18 with the finger tip engaged
 20 against an end surface 28 which includes an exit face
 21 26 of the optical fibre 10. The finger is then pressed
 22 downwardly against a resilient bias to enable a
 23 standardised contact to be obtained between the skin
 24 and the acoustic transducer. The finger tip may first
 25 be dipped in water or coated with an aqueous gel to
 26 improve the acoustic coupling.

27
 28 Referring to Figs 3 and 4, in this preferred
 29 arrangement the acoustic transducer comprises a semi-
 30 cylindrical piezoelectric transducer 30. The
 31 transducer 30 is provided with a backing member 32 of
 32 lead or another dense substance, the rear face 34 of
 33 which is shaped in irregular curves. The use of the
 34 semi-cylindrical transducer 30 maximises the area for
 35 reception of acoustic energy from the finger, while the
 36 use of a dense backing material minimises ringing

1 effects within the transducer. Additionally, the rear
2 face 34 is shaped as shown to reduce reflection of
3 acoustic energy back towards the piezo crystal.

4

5 Fig 3 also shows the finger rest biased upwardly by the
6 use of constant tension springs 38.

7

8 Fig 5 illustrates schematically the apparatus of Figs.
9 2 and 3 embodied in a self-contained, portable blood
10 monitoring apparatus including a user readout 40. An
11 apparatus of this nature allows a diabetic to monitor
12 blood glucose concentration in a convenient manner, as
13 frequently as may be desired, and in a painless and
14 discreet manner.

15

16 Other forms of photoacoustic sensor head are possible
17 within the scope of the present invention. For
18 example, Fig. 6 shows an arrangement in which a light
19 guide 50 and an acoustic transducer 52 are applied to a
20 finger 54 by means of a hinged clamp member 56. Fig. 7
21 shows a finger 60 engaged by a light guide 62 and an
22 acoustic transducer 64 which are carried on a moveable
23 assembly 66 with the finger 60 being trapped between
24 the moveable assembly 66 and a fixed anvil 68.

25

26 It is also possible to arrange the sensor head to co-
27 operate with a soft tissue surface of the body, for
28 example a soft part of the abdomen. Figs. 8a and 8b
29 show an arrangement in which a cup shaped member 70,
30 suitably of rubber, causes a light guide 72 and an
31 acoustic transducer 74 to be contacted with a bulge of
32 soft tissue 76 which may for example be drawn into
33 contact by means of a partial vacuum within the member
34 70 caused by suction through a conduit 78, or by other
35 mechanical or adhesive means.

36

1 A somewhat similar arrangement is shown in Fig. 9 in
2 which a planar mount 80 carrying a light guide 82 and
3 acoustic transducer 84 is secured to a soft area of
4 body by means of surgical adhesive 86.

5
6 Referring to Fig. 10, one method of performing
7 measurement on an ear lobe involves placing the ear
8 lobe between a fixed plate 87 and a movable plate 88.
9 The acoustic detector 89 is mounted partially
10 perpendicular that is at an acute angle, to the beam
11 axis defined as line going from the center of a lens 90
12 to the center of a window 91. It has been found that
13 the system works satisfactorily with the detector 89 at
14 an angle or 45° to the beam axis. The window 91 and
15 the detector 89 are placed in direct contact with the
16 ear and the opposite plate 88 places pressure on the
17 ear using a suitable mechanism (not shown). This
18 particular embodiment of the ear interface apparatus
19 incorporates an alignment ring 92 which is temporarily
20 attached to the ear and fits over the window housing 91
21 to aid in aligning ear into the same location every
22 time.

23
24 Referring to Fig. 11, one method of combining light
25 sources into the instrument is to use a mechanical
26 housing 93 with several holes used to align lenses 95
27 and laser diodes 94. The housing shown uses a
28 hexagonal array of seven holes. The sources and lenses
29 are arranged in such a way that they all focus to the
30 same location 96 which could be on the surface of the
31 body part. This design does not show the inclusion of
32 beamsplitters and reference detectors but they can be
33 added in an alternative arrangement.

34
35 An alternative method of combining several sources into
36 one beam is shown in Fig. 12. Several laser diodes 97

1 are shown coupled to individual fiber optic cables 131.
 2 These cables 132 are combined using a fiber Wavelength
 3 Division Multiplexer (WDM) 98. Alternative combination
 4 methods exist including couplers and multi-fiber
 5 bundles. The combined light exits the WDM 98 in a
 6 single fiber 104 and terminates at the focal point of a
 7 lens 131. This end of the fiber is imaged to the end
 8 of the finger 103 to a spot 102 using another lens 130.
 9 Some of the light is split off the main beam using a
 10 beam splitter 100 and focused onto a reference detector
 11 101 using another lens 99. Additional reference
 12 detectors and/or beamsplitters can be added to the
 13 distribution system without changing its function.
 14 Alternatively a reference detector could look directly
 15 at the body part to measure the light reflecting off
 16 the surface, as a measure of the overall light energy
 17 entering the body part.

18
 19 Referring to Fig. 13, another method of using a finger
 20 as the body part and including removable inserts is
 21 shown. A finger 105 is inserted into an insert 106
 22 that is used to customize the finger holder to a
 23 particular finger. The moulded insert 106 is placed
 24 into a housing 107. The finger 105 is placed against a
 25 semi-cylindrical acoustic detector in a module 108 which
 26 is also attached to the housing 107. A cover 109 for
 27 the housing 107 contains a mechanism 111 to apply
 28 constant force to the finger 105. The light beam 110
 29 is introduced into the finger 105 using a suitable
 30 optical distribution system (not shown). Fig. 13A shows
 31 the module 108 in greater detail. A base 200 carries a
 32 part-cylindrical piezo transducer 202 on a support 204.
 33 206 indicates a coaxial connector to communicate the
 34 transducer signal.

35
 36 Fig. 14 shows a schematic of an alternative to the

vacuum arrangement shown in Figs. 8 and 9. In this system a photoacoustic reader 121 is placed against the skin 113 with a semi-spherical detector 112 in contact with the skin 113. A vacuum pump 115 and vacuum seal 116 create a negative pressure and pull the skin 113 against the detector 112. Processing electronics 119 energizes light sources 118 and an optical distribution system 117 routes the light to the body part through a hole in the top of the semi-spherical detector 112. The optical distribution system 117 directs a small portion of the light to a reference detector 114. The processing electronics 119 measures the signal from the acoustic detector 112 and the reference detector 114 for each optical source 119 and calculates the glucose value. The value is displayed on a display 120.

Fig. 15 shows a similar system 125, only using another type of optical distribution system 127. Again a vacuum pump 123 creates a negative pressure which draws the skin up to an acoustic detector 122. Processing electronics 124 signals light sources in optical distribution system 127 to illuminate and a signal is generated at acoustic detector 122. The processing electronics 124 calculates the proper value and displays it on a display 126.

Fig. 16 shows an alternative arrangement of a photoacoustic reader. In this system 128, the vacuum system is replaced with an ear squeeze mechanism 129 which applies pressure to the ear. An acoustic detector 130 detects the signals from the ear lobe.

In the most straightforward forms of the invention, a single analyte such as glucose in blood can be measured by using light of selected wavelengths and by measuring the area or the amplitude of the received acoustic

pulse. It is preferable to make each measurement by using a train of pulses, for example about 100 pulses, and averaging the results in order to minimise the effects of noise and pulse effects in the blood flow.

The accuracy of the detection system is governed, in part, by the Signal to Noise Ratio (SNR) of the system. Variations in the intensity and duration of the light source can cause the acoustic signal to contain variations. A normalization technique, such as taking the ratio of the acoustic signal to the optical signal, can significantly reduce the effect of the source variations, thereby improving the signal to noise ratio of the system. The optical signal can be measured with a reference detector, or several reference detectors, one for each source or one for a wavelength range. An equation describing this type of normalization follows:

$$\text{Normalized Signal} = \frac{\text{Acoustic Signal}}{\text{Optical Signal}}$$

In some cases the relationship between the optical signal and the acoustic signal changes with wavelength and light intensity. When this is the case the accuracy of the measurement can be further enhanced by determining the energy dependence of the photoacoustic signal. This may be determined by establishing the specific relationship between the photoacoustic signal and the incident energy from a set of measurements and using this relationship to compensate for the non linear response. An equation describing this type of normalization is as follows:

$$\text{Normalized Signal} = \frac{\text{Acoustic Signal}}{\text{Incident Energy}}$$

Scaling Factor *Optical Signal +
Offset

Other normalization methods can also apply. The time interval between the optical pulse and the detection of the acoustic signal may be used to characterise physical properties such as the velocity of sound in the tissue. In addition, in another embodiment of the device the damping of the acoustic oscillations may be used to monitor the elastic properties of the tissue and, in particular, the compressibility. Both of these aspects may be used in the person to person calibration of the photoacoustic response.

More complex analysis of the received acoustic energy is possible. For example, a time-gating technique may be used to derive measurement at varying depths within the tissue being examined. Alternatively, an array of detectors can be employed to determine the profile of the absorption of the acoustic signal at different depths and locations. This depth profile will change with the absorption coefficient and could be used as additional information to determine the analyte concentration. It is also possible to derive information relating to a number of analytes of interest by more sophisticated analysis of the received acoustic energy wave forms, for example by analysis of the frequency spectrum by Fourier transform or wavelet analysis techniques.

Alternatively, or in combination with the frequency techniques and multiple detectors, multiple light sources can aid in the determination of the concentration of a number of analytes.

There are a number of tissue features which may vary

1 from person to person or with in the same person over
2 time which impact the photoacoustic signal observed.
3 To obtain an accurate measurement of a given analyte,
4 such as glucose, it may be helpful to also determine
5 the concentration of other analytes such as haemoglobin
6 which may act as interferants. One approach is to
7 generate several distinct photoacoustic signals using
8 excitation light of several different wavelengths. For
9 example, excitation light of a wavelength of which
10 haemoglobin absorbs strongly but glucose has little if
11 any absorption could be used to obtain a measure of the
12 haemoglobin concentration with which to normalize the
13 effect of haemoglobin on measurements made on different
14 persons or on the same person at different times.
15 These measurements which are to be normalized might be
16 based on the photoacoustic signal generated by light of
17 a wavelength at which glucose absorbs.

18
19 It is also possible to measure the concentration of
20 such interferants by other means, such as infrared
21 light absorption, and thus normalize or correct the
22 photoacoustic signal representative of the desired
23 analyte for variations in these interferants. Thus,
24 for example, the photoacoustic signal representative of
25 glucose could be corrected for variations in
26 haemoglobin concentration determined by optical
27 absorption techniques such as those taught in US Patent
28 No 5,702,284.

29
30 For the reliable and reproducible determination of
31 glucose a signal to noise ratio of at least 10,000 is
32 recommended. In this regard water is typically present
33 in human tissue of a concentration of about 50 molar
34 while glucose is present at a concentration of about 5
35 millimolar in a normal individual.

36

1 Apparatus and method embodying the present invention
2 have been found to yield accurate and repeatable
3 results. In the case of blood glucose measurement, the
4 clinical range of glucose concentration is
5 approximately 5-10 m mol/l in healthy subjects, and up
6 to 40 m mol/l in diabetics. An analysis based on
7 simple absorption models suggests that the change in
8 photoacoustic signal over this range might be as little
9 as 0.2%. The present invention has been found to
10 provide a change in photoacoustic signal of up to 140%
11 for a change in glucose concentration of 15m mol/l.
12

13 The precise mechanisms involved are not at present
14 fully understood. It is believed, however, that
15 absorption occurs primarily in body plasma and is
16 modified by the presence of glucose, and that this
17 affects beam geometry.
18

19 Example
20

21 The blood glucose levels of three individuals, one
22 normal individual, one type 1 diabetic and one type 2
23 diabetic, were followed over a two hour period
24 following each individual taking about 75 grams of
25 glucose orally in an aqueous solution by both
26 photoacoustics and direct blood measurement. The
27 results are reported in Figures 17, 18 and 19.
28 Photoacoustic measurements were made every five minutes
29 and blood measurements were made every ten minutes. The
30 blood samples were venous blood samples analysed by the
31 standard glucose oxidase method using a Yellow Springs
32 instrument. The error bands for the blood measurements
33 were derived from the literature accompanying the
34 testing instrument while those for the photoacoustic
35 results were based on the averages taken over 1000
36 pulses. The results were obtained from a configuration

similar to that illustrated in Figure 1 in which 10 was an end of a 1 km multimode fibre optic cable which was placed against the finger 12. The other end received 600 nanosecond pulses of 1040 nanometer light from a Q switched Nd:YAG laser delivering 2.7 micro joules per pulse for each measurement. Raman interactions in the fibre caused the production of light at additional wavelengths as set forth in the following table:

Wavelength in nm	Average pulse energy in microJoules	Pulse width in ns	Approximate bandwidth in nm
1064	2.7	600	4
1120	2.25	500	6
1176	2.0	450	8
1240	1.5	425	12
1308	0.85	400	15
1390	0.3	350	20
1450	0.1	350	20
1500	0.2	350	20
1550	0.18	360	20

The resulting photoacoustic signal was detected by a 5mm disc transducer with a lead backing and fed to an amplifier and an oscilloscope. The transducer was generally placed as 16 in Figure 1 but was not

1 precisely parallel to the beam axis; its detection
2 plane was at an angle of about 20 degrees to the beam
3 axis. The photoacoustic signal was evaluated in terms
4 of the difference in voltage signal from the positive
5 peak of the compression to the negative peak of the
6 relaxation of the acoustic pulse.

7
8 The change in photoacoustic response correlated well
9 with the change in blood glucose concentration over the
10 two hour measurement period. A correlation of 0.89 was
11 achieved on samples ranging from 4 to 35 mmol/l.

12
13 Other modifications and improvements may be made to the
14 foregoing embodiments within the scope of the present
15 invention as defined in the claims.

16

1 CLAIMS

- 2
- 3 1. A sensor head for use in photoacoustic in vivo
4 measurement, comprising a housing shaped to engage
5 a selected body part, light transmission means
6 terminating in said housing so as to transmit
7 light energy from a light source to enter the body
8 part along a beam axis, and acoustic transducer
9 means mounted in the housing to receive acoustic
10 waves generated by photoacoustic interaction
11 within the body part, the acoustic transducer
12 means being disposed in the housing to receive
13 said acoustic wave in a direction of high acoustic
14 energy.
- 15
- 16 2. A sensor head according to claim 1, in which the
17 acoustic transducer means is arranged at least
18 partially perpendicular to the optical beam axis.
- 19
- 20
- 21 3. A sensor head according to claim 2, for use where
22 the selected body part is the distal portion of a
23 finger, in which the housing includes a generally
24 half-cylindrical depression in which the finger
25 may be placed with the light transmission means
26 aimed at the end of the finger.
- 27
- 28 4. A sensor head according to any preceding claim, in
29 which the acoustic transducer means comprises a
30 piezoelectric transducer which is of a semi-
31 cylindrical shape.
- 32
- 33 5. A sensor head according to any preceding claim, in
34 which the acoustic transducer means comprises a
35 piezoelectric transducer which is provided with a
36 backing of lead or other dense material.

- 1 6. A sensor head according to claim 5, in which said
2 backing has a rear surface shaped to minimise
3 internal acoustic reflection.
4
- 5 7. A sensor head according to any of claims 1 to 4,
6 in which the transducer means comprises a
7 capacitor-type detector.
8
- 9 8. A sensor head according to any of claims 1 to 4,
10 in which the transducer means comprises a
11 piezoelectric transducer arranged generally
12 perpendicular to the optical axis to detect the
13 acoustic wave which is propagating in a direction
14 opposite to the direction of propagation of the
15 light beam.
16
- 17 9. A sensor head according to claim 8, in which the
18 transducer is part-spherical with an aperture to
19 allow access for the light beam.
20
- 21 10. A sensor head according to any preceding claim,
22 including a surface wave detector for
23 characterizing tissue properties.
24
- 25 11. A sensor head according to any preceding claim,
26 including means for ensuring a consistent contact
27 pressure between a selected body part and the
28 acoustic transducer means.
29
- 30 12. A sensor head according to claim 11, for use where
31 the selected part is the distal portion of a
32 finger, said means being provided by mounting a
33 portion of the housing engaged by the finger in a
34 resiliently biased fashion against the remainder
35 of the housing, and providing means to ensure that
36 measurement is effected when a predetermined force

1 or pressure is applied by the subject against the
2 resilient bias.

3
4 13. A sensor head according to claim 11, for use where
5 the selected part is the earlobe, said means being
6 provided by two plates, between which the earlobe
7 may be placed, and means for pressing the plates
8 together to apply pressure to the ear.

9
10 14. A sensor head for use in photoacoustic in-vivo
11 measurements, comprising a housing shaped to
12 receive a removable insert; a removable insert
13 that engages a selected body part, the insert
14 being fitted to an individual, allowing for a
15 range of sizes of body parts to be used; light
16 transmission means terminating in or near said
17 removable insert so as to transmit light energy
18 from a light source to enter the body part along a
19 beam axis; and an acoustic transducer means
20 mounted in the housing or in the removable insert
21 to receive acoustic waves generated by
22 photoacoustic interaction within the body part,
23 the acoustic transducer means being disposed in
24 the housing or insert to receive said acoustic
25 waves in a direction of high acoustic energy.

26
27 15. An in-vivo measuring system comprising in
28 combination: a sensor head as claimed in any
29 preceding claim; a light source coupled with the
30 light transmission means; and signal processing
31 means connected to receive the output of the
32 acoustic transducer means and to derive therefrom
33 a measurement of a selected physiological
34 parameter.

35
36 16. The system of claim 15, in which the light

1 transmission means is a fiber optic distribution
2 system.

3

4 17. The system of claim 16, in which there is a
5 plurality of light sources each connected to an
6 individual fiber and the respective fibers are
7 joined by a wavelength division multiplexer or a
8 fiber coupler.

9

10 18. The system of claim 16 or claim 17, in which the
11 fiber optic distribution system terminates in
12 contact with the body part.

13

14 19. The system of claim 16 or claim 17, in which the
15 fiber optic distribution system communicates with
16 the body part via optical elements such as lenses
17 and beamsplitters.

18

19 20. The system of claim 15, in which the light
20 transmission means comprises optical elements
21 mounted in mechanical holders and arranged to
22 convey the light from the light source to a
23 location in proximity to the body part.

24

25 21. The system of claim 19 or claim 20, in which the
26 light transmission means includes at least one
27 beamsplitter arranged in the light path to direct
28 a portion of the light to a respective reference
29 detector to measure the energy of the light
30 entering the body part.

31

32 22. The system of any of claims 15 to 21, in which the
33 signal processing means is adapted to perform a
34 multi-dimensional processing method.

35

36 23. The system of claim 22, in which the signal

1 processing means is adapted to perform one of
2 Classical Least Squares or Partial Least Squares.

3

4

5 24. The system of any of claims 15 to 21, in which the
6 signal processing means comprises a Neural
7 Network.

8

9

10 25. The system of any of claims 15 to 24, in which the
11 signal processing means is operable to analyse the
12 signals for their frequency content using one of
13 Fourier Analysis and Frequency Filtering.

14

15 26. The system of any of claims 15 to 25, in which the
16 signal processing means additionally applies
17 techniques that use time information.

18

19 27. The system of claim 26, in which the time
20 information processed is the time delay from
21 source trigger.

22

23 28. The system of any of claims 15 to 25, in which the
24 signal processing means additionally applies
25 techniques that combine both frequency and time
26 information.

27

28 29. The system of claim 28, in which the signal
29 processing means performs wavelet analysis.

30

31 30. The system of any of claims 15 to 29, in which the
32 light source is a laser light source.

33

34 31. The system of claim 30, in which said laser light
35 source is selected from a pulsed diode laser, a
36 set of pulsed diode lasers, and a tunable laser

1 source.

2

3 32. The system of claim 31, for use in measuring blood
4 glucose concentration, in which the light source
5 is a laser diode with a wavelength in the range of
6 approximately 600 nm to 10,000 nm and a pulse
7 duration of the order of 5 to 500 ns.

8

9 33 The system of any of claims 30 to 32, in which the
10 light transmission means is arranged to produce a
11 spot size of the order of 0.05 mm to 0.50 mm.

12

13 34. The system of any of claims 15 to 29, in which
14 there are multiple light sources and means are
15 provided for time multiplexing the multiple
16 sources such that: each source is switched on and
17 generates an optical pulse, or a set of optical
18 pulses, the pulse, or set of pulses, generates an
19 acoustic signal that is detected by the detector,
20 and each source is pulsed in sequence until all
21 sources have been used to generate their own
22 signals.

23

24 35. The measuring system of any of claims 15 to 34, in
25 the form of a self contained system including a
26 power supply and a readout, which may be carried
27 on the person and used at any convenient time.

28

29 36. The system of claim 35, including facilities for
30 connection to a cellular telephone, two-way pager
31 or other communication device for routine
32 transmission of measurements taken to a central
33 data collection point.

34

35 37. The system of any of claims 15 to 36, further
36 including means for manipulating the body part

1 under measurement and for performing additional
 2 measurement of the tissue to obtain other
 3 information about the state of the physiology of
 4 the tissue.

5
 6 38. The system of claim 37, in which said manipulating
 7 means includes means for squeezing a body part,
 8 such as an earlobe, and means for making photo
 9 acoustic measurements at several different
 10 pressures.

11
 12 39. The system of claim 37 or claim 36, including
 13 temperature measurement means for measuring the
 14 temperature of the body site, and in which the
 15 signal processing means is arranged to apply a
 16 correction to the measurements based upon the
 17 temperature of the body site.

18
 19 40. The system of claim 39, further including means
 20 for inducing temperatures above and below ambient
 21 in the body part.

22
 23 41. The system of any of claims 15 to 40, comprising a
 24 means for storing one or both of calibration
 25 coefficients and operational parameters in order
 26 to calibrate the instrument and to set critical
 27 operational parameters.

28
 29 42. The system of claim 41, in which the signal
 30 processing means is operable to adjust the
 31 calibration coefficients and operational
 32 parameters to be specific to a particular person.

33
 34 43. The system of claim 42, when dependent upon claim
 35 14, in which the calibration coefficients and
 36 operational parameters specific to a particular

1 person are contained in a storage site located in
2 the removable insert.

3

4 44. The system of claim 43, in which additionally
5 calibration coefficients and operational
6 parameters specific to the reader system are
7 stored in the non-removable housing.

8

9 45. The measuring system of any of claims 15 to 44,
10 further including connection means for connecting
11 the measuring system to an invasive measuring
12 system for the purpose of calibrating or adjusting
13 the operational parameters of the non-invasive
14 measuring system.

15

16 46. The system of claim 45, in which the connection
17 means is selected from a cable link, IR link or
18 radio waves.

19

20 47. A method of operating a measurement system as
21 claimed in claim 34 to remove instrument drift
22 from the measurement, the method comprising the
23 steps of:

24

25 1) placing a calibration standard in the reader
26 in place of the body part;

27

28 2) measuring the signal from the standard for
29 each wavelength and storing the values in the
30 calibration storage location;

31

32 3) before making a measurement of a body part,
33 placing the calibration standard in the
34 reader;

35

36 4) measuring the signal from the standard for

1 each source;

2

3 5) comparing the just measured standard values
4 to the stored calibration values;

5

6 6) calculating correction factors for each
7 source wavelength.

8

9 7) removing the standard and placing the body
10 part in the reader;

11

12 8) measuring the signal from the body part for
13 each source; and

14

15 9) adjusting the measured values using the
16 calculated correction factors.

17

18 48. The method of claim 47, in which a further
19 correction factor is calculated for the instrument
20 temperature.

21

22 49. A method of measuring a biological parameter in a
23 subject, the method comprising the steps of:

24

25 directing one or more pulses of optical
26 energy from the exterior into the tissue of a
27 subject along a beam axis, the optical energy
28 having a wavelength selected to be absorbed
29 by tissue components of interest, thereby to
30 produce a photoacoustic interaction;

31

32 detecting acoustic energy resulting from said
33 photoacoustic reaction by means of a
34 transducer positioned to intercept acoustic
35 energy propagating in a direction other than
36 the forward direction of said beam axis; and

1 deriving from said detected acoustic energy a
2 measure of the parameter of interest.

3
4 50 The method of claim 49, in which the parameter of
5 interest is blood glucose, and the optical energy
6 has a wavelength in the range of approximately 600
7 mm to 10,000 mm and a pulse duration of the order
8 of 5 to 500 ms.

9
10 51 The method of claim 49 or claim 50, in which a
11 train of pulses is applied and the detected
12 signals are averaged to derive said measure.

13
14 52 The method of any of claims 49 to 51, in which
15 said measure is derived from the energy of the
16 detected signal.

17
18 53 The method of any of claims 49 to 52, in which the
19 optical energy is directed into a body part which
20 is substantially composed of soft tissue and free
21 of bone.

22
23 54 Apparatus for measuring a biological parameter in
24 a subject, the apparatus comprising:

25
26 means for directing one or more pulses of optical
27 energy from the exterior into the tissue of a
28 subject along a beam axis, the optical energy
29 having a wavelength selected to be absorbed by
30 tissue components of interest, thereby to produce
31 a photoacoustic interaction;

32
33 transducer means arranged to detect acoustic
34 energy resulting from said photoacoustic reaction
35 by intercepting acoustic energy propagating in a
36 direction other than the forward direction of said

1 beam axis; and

2

3 means for deriving from said detected acoustic
4 energy a measure of the parameter of interest.

5

6 55 Apparatus according to claim 54, in which said
7 directing means includes means for receiving a
8 selected body part such that the optical energy is
9 directed into a portion of the subject's body
10 which is substantially free of bone.

11

12 56 A method of correcting measurement of an analyte
13 based on a photoacoustic signal obtained from a
14 living being comprising determining the
15 concentration of other constituents in the being
16 which have a significant effect on the
17 photoacoustic signal and tend to vary from
18 individual to individual, or over time, and
19 adjusting the measurement to remove the effect of
20 variations in the concentrations of said other
21 constituents.

22

23 57 The method of claim 56 in which the analyte is
24 glucose.

25

26 58 The method of claim 57 in which the concentration
27 of haemoglobin is determined and used to adjust
28 the measurement.

29

30 59 A method of establishing a photoacoustic signal
31 obtained from a living being comprising using the
32 ratio of the acoustic signal obtained to the
33 optical signal which generated the acoustic signal
34 to determine the concentration of an analyte
35 present in said being.

36

1 60 The method of claim 59 in which the analyte is
2 glucose.

3
4 61 A method of normalizing a photoacoustic signal
5 obtained from directing an optical beam on the
6 tissue of a living being comprising determining
7 the dependence of the photoacoustic signal on the
8 energy of the optical beam from a series of
9 measurements at different energies for the type of
10 tissue involved.
11
12
13